NCI/ICHDB/OK-82/05

PB82-922905

International Cancer Research Data Bank Program

National Cancer Institute

ONCOLOGY OVERVIEW

Selected Abstracts on

Dioxins and Dibenzofurans in Carcinogenesis

September 1982

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

National Institutes of Health

ONCOLOGY OVERVIEWS are a service of the International Cancer Research Data Bank (ICRDB) Program of the National Cancer Institute, intended to facilitate and promote the exchange of information between cancer scientists by keeping them aware of literature related to their research being published by other laboratories throughout the world. Each *ONCOLOGY OVERVIEW* represents a survey of the literature associated with a selected area of cancer research. It contains abstracts of articles which have been selected and organized by researchers associated with the field.

The abstracts published in *ONCOLOGY OVERVIEWS* are obtained from CANCERLINE, an on-line cancer information system created by the ICRDB Program in cooperation with the National Library of Medicine. Abstracts from the CANCERLINE data base, which is updated monthly with new articles abstracted from over 3000 journals, can be retrieved via on-line computer terminals at several hundred locations in the U.S. and other countries. Any organization linked to the MEDLARS/MEDLINE system at the National Library of Medicine has access to the CANCERLINE data base Occasionally, consultant reviewers identify articles of special significance to the topic of an *ONCOLOGY OVERVIEW*, which are not in CANCERLINE. These articles are represented in the *ONCOLOGY OVERVIEW* by bibliographic citations, as no abstracts are available.

This *ONCOLOGY OVERVIEW* is sent automatically to researchers in the subject area who are identified on the basis of current research project descriptions submitted to an ICRDB-supported Current Cancer Research Project Analysis Center (CCRESPAC). We encourage all cancer researchers to provide a complete and current project description to CCRESPAC. If you have not recently supplied such a description to an agency or official representative providing input to this program (i.e., NIH, American Cancer Society, Cancer Center Directors, etc.), you may obtain forms and additional information about data input from the ICRDB Program Office address listed below.

ONCOLOGY OVERVIEWS may also be obtained by any requestor at modest cost from the National Technical Information Service (NTIS), 5285 Port Royal Road, Springfield, Virginia 22161, U.S.A.

This *ONCOLOGY OVERVIEW* is prepared for the ICRDB Program by the Cancer Information Dissemination and Analysis Center (CIDAC) for Carcinogenesis. Future *OVERVIEW* editions depend on user needs and satisfaction. If this *ONCOLOGY OVERVIEW* is of value to you, please send your comments to:

CIDAC for Carcinogenesis
Franklin Research Center
Science Information Services Organization
20th and Parkway
Philadelphia, Pennsylvania 19103
U.S.A.

If you would like to receive additional ICRDB publications and learn about other ICRDB information services, please contact:

ICRDB Program Office
National Cancer Institute
Westwood Bldg., Rm. 10A18
Bethesda, Maryland 20205
U.S.A.

Each researcher receiving this publication is urged to circulate this *OVERVIEW* to colleagues, co-workers, and others who are engaged in projects related to the area covered by this publication.

Selected Abstracts
on

Dioxins and Dibenzofurans in Carcinogenesis

Thomas J. Slaga, Ph.D.
Consulting Reviewer

A SERVICE OF THE INTERNATIONAL CANCER RESEARCH DATA BANK (ICRDB) PROGRAM
OF THE NATIONAL CANCER INSTITUTE

TABLE OF CONTENTS

PAGE

INTRODUCTION iv

EDITORIAL COMMENTARY v

ABSTRACTS — ABSTRACT NUMBER

I. EXPERIMENTAL CARCINOGENICITY STUDIES OF DIOXINS AND DIBENZOFURANS

A. Carcinogenicity of Dioxins and Dibenzofurans in Experimental Animals 1-19

B. Modification of Carcinogenicity of Dioxins and Dibenzofurans in Experimental Animals 20-28

II. EXPERIMENTAL ANIMAL STUDIES OF THE METABOLIC AND TOXICOLOGIC EFFECTS OF DIOXINS AND DIBENZOFURANS

A. Toxicologic Effects Induced by Dioxins and Dibenzofurans to Experimental Animals 29-40

B. Modification of Toxicologic Effects Induced by Dioxins and Dibenzofurans to Experimental Animals 41-42

C. Induction of Mixed Function Oxidases by Dioxins and Dibenzofurans to Experimental Animals 43-68

D. Other Metabolic Effects Induced by Dioxins and Dibenzofurans by Experimental Animals 69-75

III. METABOLIC EFFECTS OF DIOXINS AND DIBENZOFURANS IN IN VITRO SYSTEMS 76-88

IV. INTERACTION OF DIOXINS AND DIBENZOFURANS WITH RECEPTORS AND MACROMOLECULES 89-98

V. EPIDEMIOLOGIC REPORTS ON THE EFFECTS OF EXPOSURE TO DIOXINS AND DIBENZOFURANS 99-106

VI. ENVIRONMENTAL OCCURRENCE, PUBLIC HEALTH ISSUES AND REGULATIONS CONCERNING DIOXINS AND DIBENZOFURANS 107-111

SUBJECT INDEX

AUTHOR INDEX

READEX FICHE

INTRODUCTION

This ONCOLOGY OVERVIEW on "Dioxins and Dibenzofurans in Carcinogenesis" includes abstracts selected from the CANCERLINE data base referencing articles published mainly during 1975-1981. Selected information dating back to the 1960's is included for historical perspective. The strategy used for the on-line data base search is available on request from the CIDAC office and can be entered at any MEDLARS/MEDLINE terminal in order to obtain continuing updates in this area.

This OVERVIEW includes all aspects of the toxicity, carcinogenicity, cocarcinogenicity, tumor promoting activity and anticarcinogenicity of dioxins and dibenzofurans as well as the effects of these agents on enzyme induction, especially those enzymes involved in the metabolism of chemical carcinogens. The role of the binding of dioxins and dibenzofurans to specific cytosol receptors in the induction of aryl hydrocarbon hydroxylase is also included. In addition, the environmental occurrence of dioxins and dibenzofurans and the effect of human exposure are presented.

This OVERVIEW was prepared by Thomas J. Slaga, Ph.D. of Oak Ridge National Laboratory, Oak Ridge, Tennessee, Anne W. Scott, Ph.D. and Steven J. Frank, Ph.D. of the CIDAC for Carcinogenesis Information, The Franklin Research Center, Philadelphia, Pennsylvania.

EDITORIAL COMMENTARY

The following commentary focuses on dioxins and dibenzofurans in carcinogenesis with some discussion on their disposition, toxicologic effects and enzyme inducing capabilities in animals.

The dioxins and dibenzofurans are part of a large series of aromatic hydrocarbons including dibenzo-p-dioxins, dibenzofurans, azo- and azoxy-benzenes, biphenyls and naphthalenes which when polyhalogenated, produce a similar and characteristic pattern of toxic responses (1). 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD), an extremely potent toxin, is the most widely studied and can be considered as the prototype of the dioxins and dibenzofurans. The extraordinary toxic potency of TCDD was first recognized by Kimmig and Schultz (2) who identified TCDD as the cause of an epidemic of acneform lesions of the skin of industrial workers involved in the production of the herbicide 2,4,5-trichlorophenoxyacetic acid. TCDD is a trace contaminant formed in the commercial synthesis of this herbicide. The polychlorinated dibenzofurans are found as contaminants in commercial polychlorinated biphenyls and in chlorinated phenol mixtures (1). They have also been detected in fly ash and flue gases of incinerators as well as in certain trichlorophenol-derived herbicides and in treated wood (1). The dioxins and dibenzofurans have no known industrial use but are widespread in the environment because they are contaminants of widely used compounds.

The cause for public health concern over the widespread use of chemicals contaminated with dioxins and dibenzofurans is well documented (1). A general exposure of the public to TCDD occurred as a result of the herbicide spraying program in Vietnam in the 1960's; the explosion in a chemical plant near Seveso in Italy in July of 1976 resulted in the exposure of many additional persons. The Yusho oil accident in Japan in 1968 resulted in an exposure of the public to various polychlorinated dibenzofurans (1). The whole picture of health effects in humans from these exposures to dioxins and dibenzofurans is far from complete. TCDD exposure to humans following the accident at the chemical plant near Seveso resulted in an increased chloracne frequency (3). Neurologic examinations showed both signs of idiopathic subclinical neurologic damage as well as cases of clinically detectable idiopathic polyneuropathy in adults (3). A limited percentage of idiopathic hepatomegaly was also reported. So far, immunologic investigations, cytogenetic examination, and embryomorphology analysis of embryos from cases of therapeutic or spontaneous abortions have not shown any increase in congenital abnormalities (3). It is too early to tell if there will be any increased incidence of cancer in the people exposed to these chemicals.

The exposure of experimental animals to dioxins and dibenzo-

furans produces a distinctive pattern of toxicity. Animals administered a lethal dose of TCDD show a prolonged wasting syndrome prior to death. Lymphoid involution accompanied by suppression of the cellular immune response and embryotoxicity and/or teratogenicity have been observed in all species (1). Hyperkeratosis and chloracne, edema, hyperplasia of the epithelium of the stomach, intestines and urinary bladder, and hepatocellular damage are toxic responses which occur in a limited number of species (1). The cause of death is unknown. Chloracne occurs in the skin of humans, nonhuman primates and in rabbits (1). Liver damage occurs in rats, mice and rabbits whereas edema is common in chickens and mice (1). There is an order of species sensitivity to TCDD: guinea pigs and chickens are the most sensitive, rats show intermediate sensitivity and mice show the least (1).

The distinct features of TCDD toxicity--species differences, delayed onset, chloracne formation, edema in young chickens, thymic involution, and teratogenicity--have been reported for other halogenated dibenzo-p-dioxins. Published results suggest that a dibenzo-p-dioxin congener which is toxic will elicit all of these responses if a sufficient dose is administered (4). The data on specific isomers of halogenated dibenzofurans, azo- and azoxy-benzenes and biphenyls are more limited but also suggest that congeners isosteric with TCDD will produce the same toxic syndrome (5).

Although dioxins and dibenzofurans show distinct features of toxicity in vivo, they appear to be relatively nontoxic when various cell types are exposed to very low doses in vitro. Knutson and Poland (6) reported that TCDD failed to demonstrate toxicity in twenty-three cultured cell types even when the cells were exposed to relatively high doses of TCDD for an extended period, usually a week or longer. The twenty-three cell types included primary cultures and cells from established and transformed cell lines. The lack of toxicity also occurred in cells derived from tissues and/or species which have been shown to be susceptible to TCDD toxicity in vivo (6). Examination of the cells for altered morphology, decrease in viability, or diminished growth rate revealed no toxic effect of TCDD in any cell type, including those in which TCDD stimulated the induction of aryl hydrocarbon hydroxylase activity (6). Knutson and Poland recently reported that keratinization of mouse teratoma cell line XB produced by TCDD and congeners may be a good in vitro model of toxicity and appears to be mediated by a TCDD cytosolic receptor (7).

TCDD has been reported to be carcinogenic in chronic feeding experiments in rats (8). Kociba et al (8) reported that a dietary intake of 0.1 ug/kg/day for two years resulted in an increase number of hepatocellular carcinomas and squamous cell carcinomas of the lung, hard palate and nasal turbinate in female Spraque-Dawley rats. Lifetime feeding of TCDD equivalent to 0.001 and 0.01 ug/kg/day produced no increase in tumor incidence in rats. Innes et al (9) reported on a long-term carcinogenicity

study conducted in mice given 2,4,5-trichlorophenoxyacetic acid contaminated with a level of TCDD sufficient to supply approximately 0.27 ug TCDD/kg/day. Neither of the two straing of mice which were tested had an increase in tumors as a result of the treatment (9). When TCDD was applied topically to mice, Berry et al (10) found that it did not have carcinogenic activity. In addition, in a two-stage system of tumorigenesis in mouse skin TCDD did not have significant tumor initiating or promoting activity (11).

The carcinogenic potency of TCDD in rats is especially interesting in light of studies which have failed to demonstrate any covalent binding of TCDD (12) and have provided inconclusive evidence that TCDD is a weak mutagen (13). Since most chemical carcinogens are mutagenic and bind covalently to macromolecules, Pitot and coworkers (14) rationalized that the liver cancer associated with chronic administration of TCDD might arise from the promoting activity of the compound. Their studies showed that TCDD is a potent tumor promoter in a multistage hepatocarcinogenesis system in the rat (14). TCDD did not have any carcinogenic activity in their studies when given subcutaneously at a dose of 0.14 or 1.4 ug/kg once every 2 weeks for 7 months (14).

TCDD and related congeners have been reported to concentrate in the liver and to an extent in the adipose tissue of the rat (15). The half-life of TCDD in the rat following a single dose is 3 to 4 weeks, and with chronic exposure a steady state is reached in about 7 weeks (15). Because of its extreme toxicity and the very low doses which must be administered very little is known about the metabolism of TCDD. However, recent results suggest that TCDD is slowly excreted in the bile and that approximately 90% of the TCDD-derived material in the bile does not cochromatograph with the parent compound (15).

The chlorinated dibenzo-p-dioxins and dibenzofurans are potent inducers of the cytochrome P 450-mediated microsomal monooxygenases, delta-aminolevulinic acid synthetase, DT-diaphorase, glucuronyl transferase, aldehyde dehydrogenase and ornithine decarboxylase (1). The most studied of the biochemical effects produced by TCDD and its congeners is the induction of the hepatic microsomal monooxygenase activity, aryl hydrocarbon hydroxylase (AHH). This response is mediated by the reversible stereospecific binding of TCDD to a cytosol receptor protein (16). This binding protein, which is determined by the Ah locus in mice, appears to be not only the receptor for the induction of AHH activity but also for other coordinately expressed enzymes (17,18). Two toxic responses produced by TCDD and its congeners in mice, thymic involution and cleft palate formation (teratogenesis), have been shown to segregate with the Ah locus (18). This suggests that the binding of TCDD to this cytosol receptor mediates not only induction of enzymes activities, but also toxic responses to TCDD.

Since TCDD was found to be an extremely potent inducer of

both hepatic and extrahepatic microsomal mixed function oxidase activity, being approximiately 30,000 times as potent as 3-methylcholanthrene (18), Slaga and coworkers (19-21) determined the effect of TCDD and its congeners on tumor initiation by polycyclic aromatic hydrocarbons in a two-stage system of tumorigenesis in mouse skin. TCDD and its congeners, at non-toxic doses, were found to be very potent inhibitors of skin tumor initiating activity by polycyclic aromatic hydrocarbons (19-21). This inhibiting effect of TCDD correlates with the AHH inducing activity of TCDD. TCDD pretreatment decreased the covalent binding of polycyclic hydrocarbons to DNA suggesting that detoxification pathways were increased more than activating pathways (19-21). In this regard, epidermal glucuronyl transferase activity was stimulated 2- to 3-fold 3 days following TCDD treatment, whereas TCDD had little or no effect on epidermal epoxide hydrase or glutathione-S-transferase activities (20). The time course for induction of epidermal AHH and glucuronyl transferase correlated with the time course for the inhibitory effects of TCDD on tumor initiation with polycyclic hydrocarbons (20).

This commentary is not intended to be an exhaustive review of the literature. For a comprehensive review the reader is referred to an excellent document on this subject entitled "Health Effects of Halogenated Aromatic Hydrocarbons" published by the New York Academy of Sciences (1).

REFERENCES

1. Health Effects of Halogenated Aromatic Hydrocarbons, W.J. Nicholson and J.A. Moore (eds.), Annals of New York Academy of Sciences, New York, New York, Volume 320: 1-730 (1979).

2. Kimmig, J. and Schultz, K.H. Chlorinated aromatic cyclic ethers as the cause of chloracne. Naturwissenschaften 44: 337-338 (1957).

3. Pocchiari, F., Silano, V. and Zampieri, A. Human health effects from accidental release of tetrachlorodibenzo-p-dioxin (TCDD) at Seveso, Italy. In: W.J. Nicholson and J.A. Moore (eds.), Health Effects of Halogenated Aromatic Hydrocarbons, Annals of New York Academy of Sciences, New York, New York, Volume 320: 311-320 (1979).

4. McConnell, E.E., Moore, J.A., Hoseman, J.K. and Harris, M.W. The comparative toxicity of chlorinated dibenzo-p-dioxins in mice and guinea pigs. Toxicol. Appl. Pharmacol. 44: 335-356 (1978).

5. Poland, A. and Glover, E. Chlorinated biphenyl induction of aryl hydrocarbon hydroxylase activity: A study of the structure-activity relationship. Mol. Pharmacol. 13: 924-938 (1977).

6. Knutson, J.C. and Poland, A. 2,3,7,8-Tetrachlorodibenzo-p-dioxin: Failure to demonstrate toxicity in twenty-three cultured cell types. Toxicol. Appl. Pharmacol. 54: 377-383 (1980).

7. Knutson, J.C. and Poland, A. Keratinization of mouse teratoma cell line XB produced by 2,3,7,8-tetrachlorodibenzo-p-dioxin: an in vitro model of toxicity. Cell 22: 27-36 (1980).

8. Kociba, R.J., Keyes, D.G., Beyer, J.E., Carreon, R.M., Wade, C.E., Dittenber, D.A., Kalnins, R.P., Frauson, L.E., Park, C.N., Barnard, S.D., Hummel, R.A. and Humiston, C.G. Results of a two-year chronic toxicity and oncogenicity study of 2,3,7,8-tetrachlorodibenzo-p-dioxin in rats. Toxicol. Appl. Pharmacol. 46: 279-303 (1978).

9. Innes, J.R.M., Ulland, B.M., Valerio, M.G., Petrucelli, L., Fishbein, L., Hart, E.R., Pallotta, A.J., Bates, R.R., Fold, H.L., Gart, J.J., Klein, M., Mithcell, I. and Peters, J. Bioassay of pesticides and industrial chemical for tumorigenicity in mice. J. Natl. Cancer Inst. 42: 1101-1114 (1969).

10. Berry, D.L., DiGiovanni, J., Juchau, M.R., Bracken, W.M., Gleason, G.L. and Slaga, T.J. Lack of tumor promoting ability of certain environmental chemicals in a two-stage mouse tumorigenesis assay. Res. Commun. Chem. Pathol. Pharmacol. 20: 101-108 (1978).

11. DiGiovanni, J., Viaje, A., Berry, D.L., Slaga, T.J., and Juchau, M.R. Tumor initiating ability of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) and Aroclor 1254

in a two-stage system of mouse skin carcinogenesis. Bull Environ. Contam. Toxicol. 18: 552-557 (1977).

12. Poland, A. and Glover, E. An estimate of the maximum in vivo covalent binding of 2,3,7,8-tetrachlorodibenzo-p-dioxin to rat liver protein, ribosomal RNA and DNA. Cancer Res. 39: 3341-3344 (1979).

13. Wasson, J.S., Hoff, J.E. and Lopriano, N.A. A review on the genetic toxicology of chlorinated dibenzo-p-dioxins. Mutat. Res. 47: 141-160 (1977).

14. Pitot, H.C., Goldsworthy, T., Campbell, H.A. and Poland, A., Quantitative evaluation of the promotion by 2,3,7,8-tetrachlorodibenzo-p-dioxin of hepatocarcinogenesis from diethylnitrosamine. Cancer Res. 40: 3616-3620 (1980).

15. Rose, J.O., Ramsey, J.C., Wentzler, T.H., Hummel, R.A. and Gehring, P.J. The fate of 2,3,7,8-tetrachlorodibenzo-p-dioxin following single and repeated oral doses to the rat. Toxicol. Appl. Pharmacol. 36: 209-226 (1976).

16. Poland, A., Glover, E. and Kende, A.S. Stereospecific, high affinity binding of 2,3,7,8-tetrachlorodibenzo-p-dioxin by hepatic cytosol. J. Biol. Chem. 251: 4936-4946 (1976).

17. Poland, A. and Glover, E. 2,3,7,8-tetrachlorodibenzo-p-dioxin: segregation of toxicity with the AL locus. Mol. Pharmacol. 17: 86-94 (1980).

18. Poland, A., Greenlee, W.F. and Kende, A.S. Studies on the mechanism of action of chlorinated dibenzo-p-dioxins and related compounds. In: W.J. Nicholson and J.A. Moore (eds.), Health Effects of Halogenated Aromatic Hydrocarbons, Annals of the New York Academy of Sciences, New York, New York, Volume 320: 214-230 (1979).

19. Cohen, G.M., Bracken, W.M., Iyer, R.P., Berry, D.L., Selkirk, J.K., and Slaga, T.J., Anticarcinogenic effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin on benzo(a)pyrene and 7,12-dimethylbenz(a)anthracene tumor initiation and its relationship to DNA binding. Cancer Res. 39: 4027-4033 (1979).

20. DiGiovanni, J., Berry, D.L., Gleason, G.L., Kishore, G.S. and Slaga, T.J. Time-dependent inhibition by 2,3,7,8-tetrachlorodibenzo-p-dioxin of skin tumorigenesis with polycyclic hydrocarbons. Cancer Res. 40: 1580-1587 (1980).

21. Berry, D.L., Slaga, T.J., DiGiovanni, J., and Juchau, M.R. Studies with chlorinated dibenzo-p-dioxins, polybrominated biphenyls and polychlorinated biphenyls in a two-stage system of mouse skin tumorigenesis: Potent anticarcinogenic effects. In: W.J. Nicholson and J.A. Moore (eds.), Health Effects of Halogenated Aromatic Hydrocarbons, Annals of the New York Academy of Sciences, New York, New York, Volume 320: 405-414 (1979).

ABSTRACTS

I. EXPERIMENTAL CARCINOGENICITY STUDIES OF DIOXINS AND DIBENZOFURANS

A.

Carcinogenicity of Dioxins and Dibenzofurans in Experimental Animals

1. 2,7-DICHLORODIBENZO-P-DIOXIN.
National Cancer Institute
NCI, Bethesda, MD, 20014
Nat Cancer Inst Carcinog Tec Ser; (123):1-103 1979

The carcinogenicity of 2,7-dichlorodibenzo-p-dioxin (DCDD) which is found as a by-product in the manufacture of pentachlorophenol and in the herbicide 2,4,5-trichlorophenoxyacetic acid and its esters, was studied in B6C3F1 mice and Osborne-Mendel rats. DCDD was incorporated in the diet at 5,000 or 10,000 ppm for 110 wk. Survival was not decreased in DCDD-treated animals, and tumor incidence was not significantly increased in DCDD-treated rats or female mice. Although the incidence of hepatocellular tumors increased with increasing dose in male mice, the significance of this finding was questioned based on past experience in this laboratory. There were significant increases in the incidences of leukemias or lymphomas ($p = 0.006$) and hemangiomas or hemangiosarcomas ($p = 0.028$) in male mice given the high DCDD dose compared with low-dose and control groups, but the incidences of these tumors showed no increase with increasing dose, and the findings were of questionable significance. It is concluded that under the conditions of this bioassay, DCDD is not carcinogenic in Osborne-Mendel rats or female B6C3F1 mice but that it may be carcinogenic in male B6C3F1 mice. (20 Refs)

2. CHLORINATED DIBENZODIOXINS.
IARC Working Group
IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man: Some Fumigants, the Herbicides 2,4-D and 2,4,5-T, Chlorinated Dibenzodioxins and Miscellaneous Industrial Chemicals. International Agency for Research on Cancer. Lyon, France, Vol. 15, 1977.

The information available on the toxicity, teratogenicity, mutagenicity, and carcinogenicity of several chlorinated dibenzodioxin derivatives, especially 2,3,7,8-tetrachlorodibenzo-dioxin (TCDD), is reviewed. Because of the inadequacy of studies on the carcinogenicity of these substances, no final evaluation can be made. However, po administration of 2,4,5-trichlorophenoxyethanol and TCDD to Swiss H/Riop mice did increase the incidence of liver tumors in males. A review of the data on human exposure revealed an increased proportion of liver cancers in cancer patients in Hanoi, North Vietnam, after the spraying of herbicides containing TCDD was instituted. A number of cancer cases have been reported in workers occupationally exposed to TCDD, but the data are not sufficient for a thorough evaluation of the risk to man. The physical and chemical properties of the derivatives are reviewed. (174 Refs)

3. CARCINOGENESIS BIOASSAY OF CHLORINATED DIBENZODIOXINS AND RELATED CHEMICALS.
King ME, Shefner AM, Bates RR
Life Sci. Res. Div., IIT Res. Inst., Chicago, Ill.
Environ Health Perspect; 5:163-170 1972

Chlorinated dibenzodioxins were applied thrice weekly to the backs of Swiss-Webster and B6C3F1 mice and Osborne-Mendel rats, and were given orally in the daily food or water to Osborne-Mendel rats and B6C3F1 mice. For the study of promotion activity, a group of mice in the skin application study was treated with dimethyl-benzanthracene (DMBA) 1 week prior to the initiation of test compound application. In the skin application series: octachlorodibenzodioxin, dichlorodibenzodioxin, and acetone produced no significant pathology; and unsubstituted and dibenzodioxin and dioxane produced one malignant lymphoma each. In the promotion series: neither octachlorodibenzodioxin nor unsubstituted dibenzodioxin produced any significant pathology; croton oil produced neoplastic lesions of the skin and lungs; dichlorodibenzodioxin produced one plasmacytoma; acetone produced one papilloma and one malignant lymphoma; and dioxane produced neoplastic lesions of the skin, lungs, and kidney. In the oral administration studies, hepatotoxicity was the major effect noted, although one mouse exhibited bronchiolar mucosal hyperplasia. Growth depression and mortality were widespread in the animals fed octachlorodioxin, with the male mice and female rats showing the greatest sensitivity.

4. BIOASSAY OF DIBENZO-P-DIOXIN FOR POSSIBLE CARCINOGENICITY.
Carcinogenesis Testing Program
Div. Cancer Cause and Prevention, NCI, NIH, Bethesda, MD, 20014
Natl Cancer Inst Carcinog Tech Rep Ser. Vol. 122, 104 pp., 1979.

The possible carcinogenicity of dibenzo-para-dioxin (UDD) was assayed in Osborne-Mendel rats and B6C3F1 mice. UDD was administered in the feed for 110 wk to rats and for 87 or 90 wk to mice; UDD was present in the diet at concentrations of 5,000 or 10,000 ppm. Mean body wt depression, relative to controls, was observed for both treated rats and treated mice. Survival at the end of the bioassay was lower in treated female rats and treated female mice than in control female rats and mice. Sufficient numbers of treated and control animals survived long enough to be at risk from late-developing tumors. High incidences of nonmalignant hepatotoxic lesions were observed in treated rats and mice. No statistically significant positive associations between UDD administration and tumor incidence at any site were found for any treated animals. It was concluded that, under the conditions of this bioassay, UDD was not carcinogenic for Osborne-Mendel rats or B6C3F1 mice. (19 Refs)

5. RESULTS OF A TWO-YEAR CHRONIC TOXICITY AND ONCOGENICITY STUDY OF 2,3,7,8,-TETRACHLORODIBENZO-P-DIOXIN IN RATS.

Kociba RJ, Keyes DG, Beyer JE, Carreon RM, Wade CE, Dittenber DA, Kalnins RP, Frauson LE, Park CN, Barnard SD, Hummel RA, Humiston CG

Toxicology Res. Lab., Health and Environmental Res., Dow Chemical U.S.A., Midland, MI, 48640

Toxicol Appl Pharmacol; 46(2):279-303 1978

Groups of Sprague-Dawley rats were maintained for up to 2 yr on diets supplying 0.1 ug [2,193 parts per trillion (ppt)], 0.01 ug (208 ppt), or 0.001 ug (22 ppt) of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD)/kg/day. A dose of 0.1 ug/kg/day increased the incidence of hepatocellular carcinomas (female only) and squamous cell carcinomas of the lung, hard palate/nasal turbinates, and tongue, but it decreased the incidence of tumors of the pituitary, uterus, mammary gland, pancreas, and adrenal gland compared with controls. Morphological changes in hepatic, lymphoid, respiratory, and vascular tissue were seen by light and electron microscopy. The primary hepatic ultrastructural changes at this high dose level was proliferation of the rough endoplasmic reticulum. Other toxic effects included increased mortality, decreased wt gain, increased urinary excretion of porphyrins and delta-aminolevulinic acid, slight depression of erythroid parameters, and increased serum activities of alkaline phosphatase, gamma-glutamyl transferase, and glutamic-pyruvic transaminase. Rats treated with 0.01 ug/kg/day generally showed a lesser degree of toxicity, and treatment with the lowest dose caused no effects of toxicologic importance. Terminal liver and fat samples from rats of the three dosage groups contained 24,000 and 8,100, 5,100 and 1,700, and 540 and 540 ppt of TCDD, respectively. It is concluded that doses sufficient to induce severe toxicity increased the incidence of some types of neoplasms in rats and reduced the incidence of others. There was no increase in neoplasms in rats receiving sufficient TCDD during the 2-yr study to induce slight or no manifestations of toxicity. (9 Refs)

6. LONG-TERM TOXICOLOGIC STUDIES OF 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN (TCDD) IN LABORATORY ANIMALS.

Kociba RJ

Toxicology Res. Lab., Health and Environmental Res., Dow Chemical Co., Midland, MI, 48640

Ann NY Acad Sci; 320:397-404 1979

The chronic toxicity and carcinogenicity of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD: 0.001-0.1 ug/kg/day in the diet for 2 yr) were studied in male and female Sprague-Dawley rats. The highest dose level caused multiple toxicologic effects. Liver toxicity was consistently observed, and this was accompanied by morphologic changes in the lymphoid, respiratory, and vascular tissues. There was an increased incidence of hepatocellular carcinoma and squamous cell carcinoma of the lung, hard palate/nasal turbinates, and tongue at this dose level. However, the incidences of pituitary, uterine, mammary gland, pancreatic, and adrenal medullary tumors were decreased at this dose level. The incidences of other spontaneous lesions such as chronic renal disease were also decreased. A lesser degree of toxicity, primarily of the liver, was seen in animals given 0.01 ug/kg/day TCDD, but the incidence of neoplasms was not increased at this dose level. No adverse effects were seen in rats given 0.001 ug/kg/day TCDD, although the liver and fat contained 540 ppt TCDD at the termination of the study. (8 Refs)

7. INCREASED INCIDENCE OF NEOPLASMS IN RATS EXPOSED TO LOW LEVELS OF 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN.

Van Miller JP, Lalich JJ, Allen JR
Dept. Pathology, Univ. Wisconsin, Madison, WI 53706
Chemosphere; 6(9):537-544 1977

The toxicity and carcinogenicity of low dietary levels of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) were investigated in male Sprague-Dawley rats divided into groups of 10 animals each and fed diets containing TCDD at 1, 5, 50, or 500 parts/trillion (ppt; 10**-12g TCDD/g food) or 1, 5, 50, 500, or 1,000 ppb (10**-9 TCDD/g food). All animals given the three highest doses died within 2-4 wk. Necropsy revealed severe liver necrosis, cellular proliferation in the bile ducts, atrophy of the thymus and spleen, and hemorrhage in the gastrointestinal tract. Of the animals fed subacute doses (5-500 ppt and 1 or 5 ppb), 23 developed neoplasms by 78 wk. The types of tumors included squamous cell lung tumors, ear duct carcinoma, lymphocytic leukemia, retroperitoneal histiocytoma, cholangiocarcinoma, angiosarcoma, fibrosarcoma and fibroma, astrocytoma, and glioblastoma. This variety of neoplasms is not consistent with the action of many known chemical carcinogens, which suggests that TCDD may be a promotor rather than an inducer of neoplastic change. (15 Refs)

8. INCREASED INCIDENCE OF NEOPLASMS IN RATS EXPOSED TO LOW LEVELS OF 2,3,7,8-TETRACHLORODIBENZO-RHO-DIOXIN.

Van Miller JP, Lalich JJ, Allen JR
Dept. Pathology, Univ. Wisconsin, Madison, WI 53706
Chemosphere; 6(10):625-632 1977

The toxicity of 2,3,7,8-tetrachlorodibenzo-rho-dioxin (TCDD) was investigated in groups of 10 male Sprague-Dawley rats fed 1, 5, 50, or 500 parts per trillion (ppt; 10**-12 g TCDD/g food) or 1, 5, 50, 500, or 1,000 ppb (10**-9 g TCDD/g food). Animals receiving 50, 500, or 1,000 ppb TCDD died between the second and fourth week of the experiment. Autopsy revealed liver necrosis, cellular proliferation in the bile ducts, and decreased spermatogenesis. The overall incidence of neoplasms in the remaining six groups fed subacute levels of TCDD was 38% (23 animals), with no neoplasms observed in the 1-ppt group. There were 6 neoplasms in the animals fed 5 ppt (ear duct carcinoma, lymphocytic leukemia, adenocarcinoma of the kidney, malignant peritoneal histiocytoma with metastases, angiosarcoma of the skin, and Leydig cell adenoma), 3 in those fed 50 ppt (muscle fibrosarcoma, squamous cell skin tumor, brain astrocytoma), 4 in rats fed 500 ppt (muscle fibroma, skin carcinoma, kidney adenocarcinoma, and sclerosing seminoma), and 5 in animals fed 1 ppb (cholangiocarcinoma, cutaneous angiosarcoma, brain glioblastoma, 2 malignant peritoneal histiocytomas with metastases). There were 10 neoplasms in 7/10 animals fed 5 ppb (4 squamous cell lung tumors, 4 neoplastic liver nodules, and 2 cholangiocarcinomas). No neoplasms were observed in controls. (15 Refs)

9. THE GENOTOXIC EFFECTS OF 2,4,5-T.

Grant WF
Genetics Lab., McGill Univ., Macdonald Campus, Ste. Anne de Bellevue, Quebec H9X 1CO, Canada
Mutat Res; 65(2):83-119 1979

The cytogenetic, carcinogenic, and teratogenic properties of the herbicide 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) are reviewed. Commercial formulations contain up to 0.1 ppm of the contaminant dioxin (2,3,7,8-tetrachlorodibenzo-p-dioxin, TCDD), which causes birth defects and tumors in animals at levels less than 100 parts per thousand. 2,4,5-T is

a clastogen that produces chromosome aberrations, including bridges and micronuclei, in a variety of animal and plant species. In addition, 2,4,5-T induces cell enlargement, lengthens the duration of the mitotic cycle, extends DNA synthesis, induces mitosis, and causes chromosome contraction, stickiness, and sticky bridges, all at low concentrations. C mitoses, multinucleate cells, polyploidy, reduced fertility, and species resistance have also been reported. In vivo production of chromosome aberations in humans is inconclusive. The emulsifiers and solvents in commercial preparations of 2,4,5-T also induce chromosome aberrations. In greater than 20 experiments involving 15 different systems, only 3 reported 2,4,5-T to be mutagenic: 2/4 sex-linked lethal tests in Drosophila and 1/2 studies with Saccharomyces cerevisiae. In one study in which 2,4,5-T was given to mice in daily doses of 21.5 mg/kg in the diet, the herbicide did not increase the number of tumors significantly. In another study, administration of 12 mg/kg/day in the diet significantly increased the incidence of neoplastic lesions in C3Hf mice. Although the data on teratogenicity are not clear-cut, several reports suggest that 2,4,5-T is teratogenic with and without TCDD and that 2,4,5-T and TCDD may potentiate teratogenicity. (131 Refs)

10. POLYCHLORINATED DIBENZODIOXINS AND DIBENZOFURANS - COMPOUNDS OF CURRENT INTEREST.

Rappe C
Dept. Organic Chemistry, Umea Univ., S-901 87 Umea, Sweden
Lakartidningen; 16(1/2):21-24 1979

Recent studies of the toxicology of dioxins and dibenzofurans are reviewed. 2,3,7,8-Tetrachlorodioxin was found to be a potent carcinogen in experimental animals, even in small doses. 1,2,3,6,7,8-hexachlorodibenzodioxin and 1,2,3,7,8,9-hexachlorodibenzodioxin also induced tumors in experimental animals. No pronounced organ specificity was found for these compounds. Polychlorinated dibenzodioxins and dibenzofurans occur as impurities in technical products such as 2,4,5-trichlorophenol and chlorinated phenols in general, and they are formed in pyrolytic reactions as well. Exposure to these carcinogens is highest in the production of (2,4,5-trichlorophenoxy)acetic acid and other chlorophenols. An epidemiological case-control study revealed an increased incidence of malignant mesenchymal soft-tissue tumors in persons exposed to phenoxy acids and chlorophenols. The tumors may be due to these substances and/or the impurities they contain. (45 Refs)

11. ROLE OF PESTICIDES IN HEPATOCARCINOGENESIS.

Sugar J, Toth K, Csuka O, Gati E, Somfai-Relle S
Res. Inst. Oncopathology, Budapest, Hungary
J Toxicol Environ Health; 5(2/3):183-191 1979

The carcinogenicity of the herbicide 2,4,5-trichlorophenoxyethanol (TCPE), which is contaminated with 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), was tested in Swiss mice. Doses of 0.7-70.0 mg/kg TCPE containing 0.00007-0.007 ug/kg TCDD were administered by gastric intubation once a week over a period of 1 yr. The incidence of liver tumors was doubled only in males given the two highest doses of TCPE (67.0 and 70 mg/kg); the tumor incidence was 48% and 58%, respectively, compared with 26% in controls. Reduction of the TCPE and TCDD doses to 1/10 and 1/100 of the max tolerated dose resulted in a reduced incidence of liver tumors to levels similar to that of controls. When two groups of mice were given the same dose of TCPE but hundredfold different doses of TCDD, no significant differences in the incidence of liver tumors resulted, indicating that TCDD in this dose range (0.0007-0.07 ug/kg) did not influence tumor frequency and that TCPE was responsible for the tumor-enhancing effect. There was no predominance of any histological type of hepatocellular tumor, and cirrhosis never preceded tumor development. When the in vivo data were compared with data on the induction of microsomal aryl hydrocarbon hydroxylase and biphenyl 2-hydroxylase activities by TCPE and TCDD, there was no correlation between the carcinogenicity of the drugs and their ability to induce these two enzymes. (26 Refs)

12. TUMOR-INITIATING ABILITY OF 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN (TCDD) AND AROCHLOR 1254 IN THE TWO-STAGE SYSTEM OF MOUSE SKIN CARCINOGENESIS.

DiGiovanni J, Viaje A, Berry DL, Slaga TJ, Juchau MR
Dept. Pharmacology, Sch. Medicine, Univ. Washington, Seattle, WA 98195
Bull Environ Contam Toxicol; 18(5):552-557 1977

The tumor-initiating ability of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) and Arochlor 1254, a polychlorinated biphenyl, was studied using the two-stage, initiation-promotion system of carcinogenesis in mouse skin. The effects of simultaneous administration of these substances with 7,12-dimethylbenz[a]anthracene (DMBA), a highly potent initiator in this system, were also investigated. When TCDD was administered alone at a dose of 2 microg/mouse, only weak initiating ability was observed after promotion for 32 wk. When TCDD and DMBA were given together, the effect was approx additive. Arochlor 1254, at a dose of 100 microg/mouse, also had weak tumor-initiating capacity after promotion for 32 wk with 12-0-tetradecanoylphorbol-13-acetate (TPA). A slight increase in the number of tumors was observed after 32 wk of concurrent administration of DMBA and Arochlor 1254. These results indicate that both Arochlor 1254 and TCDD are weak tumor-initiators in the two-stage system of mouse skin tumorigenesis, and that when administered concurrently with a known carcinogen in this system, the response to them is only slightly enhanced. (22 Refs)

13. CARCINOGENIC BIOASSAY OF THE HERBICIDE, 2,4,5-TRICHLOROPHENOXYETHANOL (TCPE) WITH DIFFERENT 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN (DIOXIN) CONTENT IN SWISS MICE.

Toth K, Sugar J, Somfai-Relle S, Bence J
Res. Inst. Oncopathology, Budapest, Hungary
Prog Biochem Pharmacol; 14:82-93 1978

The carcinogenic effects of the herbicide of 2,4,5-trichlorophenoxyethanol (TCPE) and its contaminant dioxin were studied in male and female outbred Swiss-H/Riop mice. The acute po LD50 for TCPE contaminated with 0.1 ppm dioxin was 1,320 mg/kg, and the max tolerable dose was 70 mg/kg. In male mice given 70 mg/kg TCPE, the incidence of liver tumors was doubled at the end of the second year compared to experiment controls. The tumor frequency was not affected by increased levels of dioxin. A decreased TCPE dose resulted in a decreased liver tumor incidence, even when the concentration of dioxin was increased. Cirrhosis never preceded the development of tumors. The liver tumors were classified histologically as hepatomas with eosinophilic globular bodies and no cellular atypia or metastasis; hepatomas without inclusions; and trabecular-type hepatocellular carcinomas that were able to metastasize. The histologic pattern was not related to drug administration. Mice treated with dioxin (10(-3) mg/kg) alone developed postnecrotic liver cirrhosis or focal necro-

sis in some cases, but the tumor incidence was not elevated above control levels. The use of TCPE as a herbicide in accordance with factory regulations and the consumption of TCPE-treated products do not appear to pose a carcinogenic risk for the consumer. (12 Refs)

14. CARCINOGENICITY TESTING OF HERBICIDE 2,4,5-TRICHLOROPHENOXYETHANOL CONTAINING DIOXIN AND OF PURE DIOXIN IN SWISS MICE.

Toth K, Somfai-Relle S, Sugar J, Bence J
Res. Inst. Oncopathology, Rath Gyorgy 7-9, H-1122 Budapest, Hungary
Nature (Lond); 278(5704):548-549 1979

The carcinogenic effects of 2,4,5-trichlorophenoxyethanol (TCPE) contaminated with dioxin (DO) and of DO alone (both compounds administered weekly by gastric tube for 1 yr) on male and female Swiss mice were studied. The LD50 of an acute po dose of TCPE containing 0.1 ppm DO was 1,320 mg/kg, and the max tolerated dose was 70 mg/kg. The only difference in tumor incidence between the treatment groups and controls was in that of liver tumors in male mice. Liver tumor incidence in Groups 1 (67 mg/kg TCPE + 0.112 ug/kg DO), 2 (70 mg/kg TCPE + 0.007 ug/kg DO), and 10 (0.7 ug/kg DO) was twice that in the respective control groups (vehicle alone). Liver tumor incidence in Group 5 (7 mg/kg TCPE + 0.0007 ug/kg DO) and Group 6 (0.7 mg/kg TCPE + 0.00007 ug/kg DO) did not differ from that in the respective control groups. There were no significant differences in the frequency of liver tumors between Groups 1 and 2 or Groups 4 (7 mg/kg TCPE + 0.07 ug/kg DO) and 5. There was also no significant difference in liver tumor incidence between Groups 2 and 11 (0.007 ug/kg DO), although they received the same amount of DO. The incidence in Group 10 was twice that in control Group 12. Spontaneous and induced liver tumors were not histologically different, and the ratio of benign hepatomas to hepatocellular carcinomas was not affected by treatment. Av life-span was decreased considerably in Group 9, which received the highest dose of DO (7 ug/kg). DO contamination and exposure to TCPE during its production and use should be controlled and reduced. (22 Refs)

15. RESEARCH RELATED TO THE HERBICIDE BUVINOL, ESPECIALLY FOR POSSIBLE CARCINOGENICITY.

Sugar J, Toth K, Somfai-Relle S, Bence J
Res. Inst. Oncopathology, Budapest, Hungary
IARC Sci Publ; (25):167-172 1979

The toxicity and carcinogenicity of the new herbicide Buvinol, which contains 2,4,5-trichlorophenoxylethanol (TCPE), were evaluated in male and female Swiss mice. In long-term carcinogenicity tests, the po administration of the max tolerated dose (70 mg/kg) of TCPE, contaminated with 0.1 ppm 2,3,7,8-tetrachlorodibenzo-p-dioxin (dioxin), increased the incidence of liver tumours in male mice, lower doses of TCPE (7.0 and 0.7 mg/kg) and dioxin did not influence tumour frequency. The tumors induced by 70 mg/kg TCPE + 0.1 pm dioxin included 71 hepatomas, 34 hepatocellular carcinomas, and 5 cholangiohepatocellular carcinomas. Exposure of workers to TCPE during its production or use should be controlled and reduced. (8 Refs)

16. CARCINOGENIC ACTIVITY OF ANALOGUES OF P-DIMETHYLAMINOAZOBENZENE.

Brown EV
U. Kentucky, Lexington
Acta Unio Int Cancrum; 19(3-4):531-533 1963

It has been shown that there is a wide range of activity in the six possible isomers of the monopyridine and pyridine-N-oxide analogs of p-dimethylaminoazobenzene (DAB; butter yellow). Subsequently it has been shown that the seven isomers of N,N-dimethyl-p-quinolylazoaniline and their seven N-oxides show an even greater range of activity. This report discusses the hepatocarcinogenic activity of the isomeric N,N-dimethyl-p-isoquinolylazoanilines and the activity of the following analogs of DAB: tetrahydronaphthaline, 2-anthracine, 1-2-anthraquinone, 2-benzothiazole, 3-diphenylthiophene, 2-dibenzofuran, 6-quinoxaline. Rough quantitative values are given for their relative tumor producing activity.

17. KERATINIZATION OF MOUSE TERATOMA CELL LINE XB PRODUCED BY 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN.

Knutson JC, Poland A
McArdle Laboratory for Cancer Research, University of Wisconsin, Madison, Wisconsin 53706
Cell (Camb); 22:27-36 1980

18. IDENTIFYING CARCINOGENS.

Hay A
Zoological Society, London, England
Nature (Lond); 269(5628):468-470 1977

At an Ecotoxicology Workshop the problems involved in the identification of carcinogens were discussed in relation to the work done on the azo dye butter yellow and the 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) that was released in the Seveso accident. Reports of these chemicals in the tests currently used to identify potential carcinogens are conflicting. Reliable short-term tests for initial screening of potential carcinogens are necessary before the more costly animal testing is begun. It has been suggested that chemicals be selected on the basis of their structural and physiochemical resemblances to known carcinogens. Butter yellow gives a negative response to the Ames test, while it gives a reproducible positive response to the Styles cell transformation test. Both tests are necessary for the screening of such chemicals. The chemistry of TCDD is not like that of any known carcinogen; however, ring epoxidation may occur in vivo and convert it into a potential carcinogen. In rats, TCDD has been shown to cause cancer of the kidney, liver and skin, and angiosarcomas. Further studies that are near completion will help to clarify these results. (no Refs)

19. THE CARCINOGENIC AND OTHER CHRONIC EFFECTS OF PERSISTENT HALOGENATED ORGANIC COMPOUNDS.

Kimbrough RD
Toxicology Branch, Center Disease Control, Dept. Health, Education and Welfare, Atlanta, GA, 30333
Ann NY Acad Sci; 320:415-418 1979

The chronic effects of persistent halogenated organic compounds are reviewed. These compounds induce mixed function oxidases and cause hepatomegaly in rodents and other mammals. The halogenated dibenzo-dioxins and hexachlorobenzene induce experimental hepatic porphyria, and the polychlorinated biphenyls (PCBs) and technical pentachlorophenyl cause adenofibrosis in rats. Adenofibrosis usually occurs concomitantly with hepatocellular carcinoma in rodents and has also been described in rats exposed to other

carcinogens such as p-dimethylaminoazobenzene. Hepatocellular tumors have also been reported in rodents after exposure to DDT, dieldrin, mirex, and Kepone, but these compounds do not produce the same type of liver pathology as PCBs. It is not known whether the experimental hepatic porphyria induced by these compounds is in any way related to the induction of hepatocellular carcinoma. Kepone and technical hexachlorobenzene have been reported to cause hyperplasia of the adrenal cortex in rats and quail. All of the halogenated above organic compounds are persistent in biologic systems, but it is not known whether the isomers that persist are the ones that are carcinogenic. Neoplastic nodules are considered to represent part of the spectrum of response elicited by hepatocarcinogens in rodents. All of the halogenated organic compounds may either prevent or enhance tumor induction by other chemicals. Most of these compounds also require activation so that dermal application would not necessarily result in tumor formation. (15 Refs)

B.
Modification of Carcinogenicity of Dioxins and Dibenzofurans in Experimental Animals

20. TIME-DEPENDENT INHIBITION BY 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN OF SKIN TUMORIGENESIS WITH POLYCYCLIC HYDROCARBONS.

DiGiovanni J, Berry DL, Gleason GL, Kishore GS, Slaga TJ
McArdle Lab. Cancer Res., Univ. Wisconsin, Madison, WI, 53706
Cancer Res; 40(5):1580-1587 1980

The effects of treating female mice with single topical doses of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) at various times before and after 7,12-dimethylbenz(a)anthracene (DMBA), benzo(a)pyrene, 3-methylcholanthrene (MCA), and (+-)-trans-7beta,8alpha-dihydroxy-9alpha,10alpha-epoxy-7,8,9,10-tetrahydrobenzo(a)pyrene were studied. TCDD, at doses of 1 ug/mouse, was applied topically 3 days prior to, 5 min prior to, or 1 day after the initiator. The application of TCDD 5 min prior to or 1 day after initiation with DMBA, benzo(a)pyrene, or MCA had little or no effect on papilloma formation. In contrast, when TCDD was applied 3 days prior to initiation with these hydrocarbons, a marked reduction in papilloma formation was observed. TCDD, applied 3 days prior to, 5 min prior to, or 1 day after initiation with (+-)-trans-7beta,8alpha-dihydroxy-9alpha,10alpha-epoxy-7,8,9,10-tetrahydrobenzo(a)pyrene produced 81, 50, and 39% inhibition of papilloma formation after 20 wk of promotion. Similar effects were observed when higher initiating doses of DMBA and the diol-epoxide were utilized. In addition, single ip does of TCDD (1 ug/mouse) 3 days prior to initiation with DMBA or MCA were highly effective at inhibiting papilloma formation. Several congeners of TCDD, lacking, possessing similar, or possessing different inducing properties, were tested for their effects on tumor initiation by DMBA. Topical application of TCDD at the doses utilized in the tumor experiments markedly induced epidermal aryl hydrocarbon hydroxylase (21-fold) 3 days after treatment. In addition, epidermal uridine diphosphoglucuronyltransferase activities were stimulated two- to three-fold 3 days following TCDD treatment. TCDD treatment had little or no effect on epidermal epoxide hydrase or glutathione S-transferase activities. The time course for induction of epidermal aryl hydrocarbon hydroxylase and uridine diphosphoglucuronyltransferase correlated with the time course for the inhibitory effects of TCDD on tumor initiation with DMBA, benzo(a)pyrene, and MCA. (Author abstract) (55 Refs)

21. 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN: POTENT ANTICARCINOGENIC ACTIVITY IN CD-1 MICE.

DiGiovanni J, Berry D L, Juchau MR, Slaga TJ
McArdle Lab. for Cancer Res., Univ. Wisconsin Medical Center, Madison, WI, 53706
Biochem Biophys Res Commun; 86(3):577-584 1979

Topical pretreatment with nontoxic doses of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), a contaminant formed in the commercial synthesis of the herbicide 2,4,5-trichlorophenoxyacetic acid, strongly inhibited the initiation of skin tumors by 7,12-dimethylbenz(a)anthracene (DMBA) and benzo(a)pyrene (BaP) in female CD-1 mice. A 1 ug dose of TCDD administered 1, 3, 5, or 10 days before DMBA treatment resulted in 86%, 91%, 94%, and 78% inhibition, respectively, of the number of papillomas formed per mouse. When doses of 0.01 or 0.1 ug/mouse of TCDD were applied 3 days prior to DMBA application, papilloma formation was inhibited by approx 80% and 90%, respectively. A 2 ug dose of TCDD was slightly more effective than the 0.1 ug dose of TCDD. Toxicity was seen only with the 2 ug dose. Similar inhibitory effects of TCDD on skin tumor initiation by BaP were also observed; however, the magnitude of the effect was slightly less than that observed with DMBA as the initiating agent. The same dependence on the time of pretreatment was noted. A 1 ug dose of TCDD given 5 days prior to initiation with BaP produced approx 65% inhibition of papilloma formation. Treatment with TCDD also produced marked induction of epidermal monooxygenase enzymes functional in the conversion of DMBA to a variety of hydroxylated products. The time course of the anticarcinogenic effects resulting from TCDD pretreatment correlated with the magnitude of this induction as well as with a significant reduction in the quantity of DMBA metabolites covalently bound in vivo to epidermal DNA and RNA but not protein. The results suggest that TCDD pretreatment gives rise to an increased rate of inactivation of the DMBA molecule relative to the rate of activation in mouse skin. (24 Refs)

22. STUDIES WITH CHLORINATED DIBENZO-P-DIOXINS, POLYBROMINATED BIPHENYLS, AND POLYCHLORINATED BIPHENYLS IN A TWO-STAGE SYSTEM OF MOUSE SKIN TUMORIGENESIS: POTENT ANTICARCINOGENIC EFFECTS.

Berry DL, Slaga TJ, DiGiovanni J, Juchau MR
Cancer and Toxicology Program, Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN, 37830
Ann NY Acad Sci; 320:405-414 1979

The ability of chlorinated dibenzo-p-dioxins, polybrominated biphenyls (PBBs), and polychlorinated biphenyls (PCBs) to modify tumor initiation in a mouse skin assay was studied in female CD-1 mice. Topical 12-O-tetradecanoylphorbol-13-acetate (TPA) caused marked inflammation and increased layers of intrafollicular epidermis (IFE). 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) caused some increase in the number of cells in the IFE; PCBs and PBBs did not affect the IFE, and 2,7-dichlorodibenzo-p-dioxin (DCDD) and 3,4',3',4'-tetrachloroazobenzene (TCAB) did not cause increased thickening of the IFE. The two biphenyls and TCDD did not promote the development of skin tumors following 7,12-dimethylbenz(a)anthracene (DMBA) initiation. Aroclor 1254 and TCDD were very weak tumor initiators, but they decreased DMBA initiation by 45% and 93%, respectively. DCDD slightly inhibited DMBA initi-

ation, and TCAB slightly enhanced it. The inhibition of DMBA initiation by TCDD was related to the ability of TCDD to induce epidermal monooxygenases, which are responsible for converting DMBA to a variety of hydroxylated products. TCDD pretreatment reduced the binding of subsequently applied DMBA to epidermal DNA and, to a lesser extent, RNA; it had no effect on the binding of DMBA to epidermal protein. (36 Refs)

23. ANTICARCINOGENIC EFFECTS OF 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN ON BENZO(A)PYRENE AND 7,12-DIMETHYLBENZ(A)ANTHRACENE TUMOR INITIATION AND ITS RELATIONSHIP TO DNA BINDING.

Cohen GM, Bracken WM, Iyer RP, Berry DL, Selkirk JK, Slaga TJ
Dept. Biochemistry, Univ. Surrey, Guildford, GU2 5XH, Surrey, England
Cancer Res; 39(10):4027-4033 1979

The effect of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) pretreatment on the skin carcinogenicity of both benzo(a)pyrene [B(a)P] and dimethylbenz(a)anthracene (DMBA) was investigated in female Sencar mice. The topical administration of 1 ug 72 hr prior to B(a)P (100 nanomol) or DMBA (10 nanomol) strongly inhibited tumor initiation by both agents. TCDD caused a marked decrease in the in vivo covalent binding of DMBA to DNA and RNA but significantly increased in vivo binding of B(a)P to DNA, with relatively little change in RNA binding. The in vivo binding of B(a)P to DNA in the absence of TCDD pretreatment was accompanied by formation of a major hydrocarbon-deoxyribonucleoside adduct, which cochromatographed with 7,8-dihydroxy-9,10-epoxy-7,8,9,10-tetrahydrobenzo(a)pyrene bound to the exocyclic amino group of guanine. The increased in vivo binding to DNA following pretreatment with TCDD did not result in the formation of detectable amounts of this adduct but did result in the formation of other, as yet unidentified, adducts. The authors suggest that the absence of the adduct of 7,8-dihydroxy-9,10-epoxy-7,8,9,10-tetrahydrobenzo(a)pyrene bound to guanine corresponds to the marked tumor-inhibitory properties of TCDD and that formation of this adduct may be a critical step in B(a)P-induced mouse skin carcinogenesis. (49 Refs)

24. LACK OF TUMOR-PROMOTING ABILITY OF CERTAIN ENVIRONMENTAL CHEMICALS IN A TWO-STAGE MOUSE SKIN TUMORIGENESIS ASSAY.

Berry DL, DiGiovanni J, Juchau MR, Bracken WM, Gleason GL, Slaga TJ
Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN, 37830
Res Commun Chem Pathol Pharmacol; 20(1):101-108 1978

Butylated hydroxytoluene (BHT), butylated hydroxyanisole (BHA), Aroclor 1254 (polychlorinated biphenyl, PCB), Firemaster-6 (polybrominated biphenyl, PBB), and 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) were tested on CD1 female mice for their tumor-promoting ability following application of 0.2 ml of a 200-nanomole soln of 7,12-dimethylbenz(a)anthracene (DMBA). At a dose of 1 mg twice weekly, neither BHT nor BHA promoted skin tumors; no tumors were induced when they were tested for carcinogenicity without DMBA initiation. PCB and PBB, at a dose of 100 ug twice weekly after DMBA application, were also inactive as promotors. TCDD was tested at a dose of 0.1 ug twice weekly; it did not promote DMBA-induced tumors and did not act as a carcinogen by itself. It did, however, result in skin rashes. None of the compounds significantly increased the intrafollicular epidermis. If the doses of the compounds were increased to levels that would lead to epidermal proliferation, their toxicity would interfere with the carcinogenic response prior to termination of the test. These results indicate that dosage may be an important factor in promotion, since some of these compounds are promotors in pulmonary and hepatic systems. (22 Refs)

25. 2,3,7,8,-TETRACHLORODIBENZO-P-DIOXIN AS COCARCINOGEN CAUSING 3-METHYLCHOLANTHRENE-INITIATED SUBCUTANEOUS TUMORS IN MICE GENETICALLY 'NONRESPONSIVE' AT AH LOCUS.

Kouri RE, Rude TH, Joglekar R, Dansette PM, Jerina DM, Atlas SA, Owens IS, Nebert DW
Dept. Biochemical Oncology, Microbiological Associates, Bethesda, MD, 20016
Cancer Res; 38(9):2777-2783 1978

The purpose of this study was to determine whether 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), at a dose (100 ug/kg ip or sc) sufficient to induce aryl hydrocarbon hydroxylase (AHH) activity and cytochrome P1-450 in genetically nonresponsive DBA/2 mice would enhance the susceptibility of these mice to 3-methylcholanthrene (3-MC) tumorigenesis. TCDD alone ip killed 30%-70% of the animals in each group of DBA/2 or responsive C57BL/6 mice, but it produced no tumors in survivors 36 wk later. TCDD given to C57BL/6 mice ip 2 days prior to or simultaneously with sc 3-MC did not affect the 3-MC carcinogenic index (which is about 60 in these mice). TCDD given to DBA/2 mice ip 2 days prior to sc 3-MC increased the carcinogenic index slightly (from 5 to 10; in these mice, the carcinogenic index of 3-MC alone is 1). When TCDD was injected simultaneously (sc, in the same vehicle) with 3-MC into DBA/2 mice, the carcinogenic index was increased markedly (from 5 to 38). In this test system, therefore, TCDD appeared to be carcinogenic. However, it is concluded that TCDD is a cocarcinogen. Its proposed mechanism of action is the induction of AHH activity and the associated P1-450 at the site of inoculation of 3-MC in genetically nonresponsive mice, thereby resulting in more efficient metabolic conversion of 3-MC to the (proximal or) ultimate carcinogen. (39 Refs)

26. THE EFFECTS OF 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN (TCDD) AND AROCLOR 1254 ON 7,12-DIMETHYLBENZ[A]ANTHRACENE METABOLISM AND TUMOR ACTIVITY IN MOUSE SKIN (MEETING ABSTRACT).

DiGiovanni J, Slaga TJ, Berry DL, Juchau MR
Dept. Pharmacology, Univ. Washington, Seattle, WA
Proc Am Assoc Cancer Res; 19:110 1978

The present study was designed to investigate the effects of pretreatment with 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) and Aroclor 1254 on the tumor-initiating activity of 7,12-dimethylbenz[a]anthracene (DMBA) in mouse skin and biotransformation (assessed with high pressure liquid chromatography - HPLC) in the same tissue. The skin tumor initiating ability of TCDD (2 microg) or Aroclor 1254 (100 microg) was very weak, producing 0.1 and 0.2 papillomas per mouse, respectively. TCDD (2 microg) and Arocior 1254 (100 microg) given topically 5 min prior to initiation with DMBA (2.56 microg) produced only slight changes in the tumor response of this compound. However, TCDD (1 microg) applied topically 3 days prior to initiation with DMBA (2.56 microg) produced significant inhibition (approx 90%). Aroclor 1254 (100 microg) produced only a slight inhibition. HPLC profiles from incubations containing C14-DMBA and epidermal homogenates (pre-

pared from mice pretreated with TCDD (1 microg) 3 days prior to sacrifice) revealed large increases in formation of phenols, diols and 7-hydroxymethyl-12-methylbenz[a]anthracene when compared with control tissues. Several peaks appeared in the diol region that were not detectably present in control profiles. Formation of 12-hydroxymethyl-7-methylbenz[a]anthracene was reduced in profiles from TCDD pretreated animals. Profiles from incubations containing tissues from Aroclor pretreated animals (100 microg, 18 hr prior to sacrifice) showed similar patterns but of much lower magnitude. The results indicate that the net effect of induction with these two compounds is to increase the inactivation relative to activation of DMBA in mouse skin.

27. DIBENZOFURAN-FREE AROCLOR 1254 AS A PROMOTER OF DIETHYLNITROSAMINE (DENA) HEPATOCARCINOGENESIS IN RATS (MEETING ABSTRACT).

Preston BD, Van Miller JP, Moore RW, Allen JR
Univ. Wisconsin, Madison, WI, 53706
Proc Am Assoc Cancer Res; 20:153 1979

Chlorinated dibenzofurans (CDF) are toxic contaminants found in most Aroclor polychlorinated biphenyl (PCB) mixtures. This study was undertaken to determine what role CDF contaminants play in Aroclor 1254 promotion of hepatocarcinogenesis. CDF-free Aroclor 1254 was prepared by adsorbing the relatively polar CDFs to activated florisil while eluting the non-polar PCB moieties with hexane. Six experimental groups, each containing 48 100 g male Sprague-Dawley rats, were established. 50 ppm diethylnitrosamine (DENA) was given in the drinking water of designated groups for 5 wk as an hepatic tumor initiator. Groups receiving promoter were given either Aroclor 1254 or CDF-free Aroclor 1254 mixed at 100 ppm in the diet for an 18 wk interval immediately following the 5 wk initiation period. The experimental groups and associated % incidence of hepatic tumors follows: I) control, 0%; II) DENA then control diet, 42%; III) water then Aroclor 1254, 0%; IV) DENA then Aroclor 1254, 97%; V) water then CDF-free Aroclor 1254, 0%; VI) DENA then CDF-free Aroclor 1254, 100%. The tumors seen in groups II, IV and VI were primarily hepatocellular carcinomas with some cholangio- and hepatocholangiocarcinomas in each group. It is concluded that the promoting ability of Aroclor 1254 is due to the PCB components and not the CDF contaminants. (no Refs)

28. QUANTITATIVE EVALUATION OF THE PROMOTION BY 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN OF HEPATOCARCINOGENESIS FROM DIETHYLNITROSAMINE.

Pitot HC, Goldsworthy T, Campbell HA, Poland A
McArdle Lab. Cancer Res., Univ. Wisconsin, Madison, WI, 53706
Cancer Res; 40(10):3616-3620 1980

In order to test the potential of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) as a promoter of hepatocarcinogenesis, rats which had received a single 10-mg/kg dose of diethylnitrosamine (DEN) following partial hepatectomy were given TCDD (0.14 and 1.4 ug/kg sc once every 2 wk) for 7 mo. Animals which received (a) only a single initiating dose of DEN after partial hepatectomy and no further treatment of (b) TCDD alone with no initiating dose of DEN exhibited relatively few enzyme-altered foci and no hepatocellular carcinomas. However, animals initiated with DEN and then given TCDD had a marked increase in enzyme-altered foci. At the higher dose of TCDD, hepatocellular carcinomas were present in five of seven rats. By means of three different enzyme markers used to evaluate the phenotypes of the enzyme-altered foci, a distinct phenotype heterogeneity of the foci was noted with a shift towards phenotypes exhibiting a greater deviation from normal liver when TCDD was given following DEN-partial hepatectomy. Quantitation of the numbers of enzyme-altered foci was performed by relating measurements made from two-dimensional tissue sections to the numbers of foci per unit vol of liver using relationships established in the field of stereology. The total vol of the liver occupied by the enzyme-altered foci, but not their number, increased with the dose of TCDD administered following DEN-partial hepatectomy. These studies demonstrate that TCDD is a potent promoting agent for hepatocarcinogenesis. (Author abstract) (43 Refs)

II. EXPERIMENTAL ANIMAL STUDIES OF THE METABOLIC AND TOXICOLOGIC EFFECTS OF DIOXINS AND DIBENZOFURANS

A.

Toxicologic Effects Induced by Dioxins and Dibenzofurans to Experimental Animals

29. CHRONIC TOXICITY OF 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN IN RATS. (MEETING ABSTRACT).

Van Miller JP, Allen JR
Univ of Wisconsin, Madison, WI 53706
Fed Proc; 36(3):396 1977

Male Sprague-Dawley rats (10 animals per group) were fed diets containing various levels of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) for 65 weeks. Acute toxic effects including severe liver necrosis, bile duct hyperplasia and edema, atrophy of the thymus and spleen, hemorrhage in the gastrointestinal tract, and decreased spermatogenesis were observed in animals receiving 1.0, 0.5 and 0.05 ppm TCDD. All of the animals in these three groups died within 4 weeks. Weight gain in groups receiving 5.0 and 1.0 ppb TCDD was significantly lower than controls, and 50% and 40% mortality, respectively, occurred over 65 weeks. The remaining groups (0.5, 0.05, 0.005 and 0.001 ppb) has an 8% mortality rate in 65 weeks. Moderate liver alterations as well as bile duct hyperplasia and edema were common in all 12 animals that died. Death of 3 of the animals in the 5.0 ppb group was attributed to aplastic anemia. In 6 of the remaining 9 animals that died neoplastic changes were observed including carcinomas of the kidney (2), liver (2) and skin (1) and an angiosarcoma. In addition, laparotomies and biopsies have indicated 2 additional neoplasms including a bile duct carcinoma and an angiosarcoma. After 18 months all of the animals will be removed from the TCDD diet and further evaluated. (Author Abstract)

30. A REVIEW OF THE GENETIC TOXICOLOGY OF CHLORINATED DIBENZO-P-DIOXINS.

Wassom JS, Huff JE, Loprieno N
Environmental Mutagen Information Center, Information Center Complex/Information Div., Oak Ridge Natl. Lab., Oak Ridge, TN, 37830
Mutat Res; 47(3/4):141-160 1978

Published and unpublished information on the genetic toxicology of chlorinated dibenzo-p-dioxins, particularly 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), is reviewed. TCDD may be formed along with other dioxin compounds during manufacture of the herbicide 2,4,5-trichlorophenoxyacetic acid, the fungicide pentachlorophenol, and the germicide hexachlorophene. Research on dioxins as potential mutagens was initiated because of their structural similarity to acridines, a class of known intercalating agents. Only four dioxins have been evaluated for mutagenicity: the di, tetra, and octachlorinated derivatives and the unsubstituted dibenzo-p-dioxin. The results of these evaluations are inconclusive. Experiments with mice suggest that TCDD may be a hepatocarcinogen because of its specific cytological effect on proliferating hepatocytes. However, the cytological effects produced by TCDD in the liver of animals may be due to the toxic effects of the short-term high dose levels administered and to the fact that TCDD tends to concentrate in the liver. The positive mutagenic and cytological effects reported with the few dioxin isomers examined seem to depend on the position of chlorine substitution, with TCDD being the most active form. Preliminary results of cytogenetic analyses of maternal blood and abortive fetal tissue from persons exposed to TCDD in Seveso, Italy (accidental release from a chemical plant), are inconclusive. However, workers exposed to the herbicides Klorinol and Buvinol, which may have varying levels of TCDD contamination, had a higher incidence of chromatid breaks in peripheral lymphocytes than nonexposed individuals. The conflicting results of mutagenicity tests with dioxins could be due to solubility problems, treatment protocols, sample purity, and the extremes in toxicity of these compounds. (70 Refs)

31. SHORT-TERM TOXICITY OF 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN IN THE RAT: MORPHOLOGICAL, ULTRASTRUCTURAL, AND ENZYMOLOGICAL STUDY OF THE LIVER.

Truhaut R, Pham-Huu-Chanh , van Haverbeck G, Azum-Gelade MC, Saint Ruf G, Lareng L
Fac. Pharm. Biol. Sci., Rene Descartes Univ., Paris, France
C R Acad Sci [D] (Paris); 279(18):1565-1569 1974

2,3,7,8-Tetrachlorodibenzo-p-dioxin (Dioxin) was admin to albino Norwegian rats and Wistar A. G rats: 50 rats received 50 ug/kg ip and 100 rats, 100 ug/kg po five x/wk for 24 d. There were no deaths until 8 d after institution of treatment, but after 22 d the mortality had reached 80%. After 18 d the liver appeared grossly normal, but microscopic examination showed pseudoacinar structures formed from accumulation of hepatocytes around canaliculi or lacunae. Examination of sections from the lungs of two rats disclosed the presence of hepatic cells in the pulmonary parenchyma. Kinetic studies of hepatic lesions revealed that none were present until 7 d after Dioxin treatment was begun. They consisted of anisokaryosis, frequent binucleation, slight cellular retraction, cytoplasmic homogenization and vacuolation of some cells. These lesions became more pronounced after 9 d, but pseudoacinar structures were not observed until the 18th d or later. The first ultrastructural changes became evident after 7 d and consisted of dilatation of the endoplasmic reticulum which gave rise to small vacuoles; myelin figures were also present. The structure of mitochondria remained almost normal until the 24th d. No apparent change occurred in succinate dehydrogenase or diphosphopuridine nucleotide-tetrazolium reductase activities, while the activity of pericanalicular adenoside triphosphatase almost completely disappeared after 3 d. These findings suggest that Dioxin may be carcinogenic. However, no accumulations of hyperbasophilic cells, considered to be the first manifestation of malignant transformation, were ever found.

32. COMPARATIVE TOXICITY OF POLYCHLORINATED BIPHENYLS AND DIBENZOFURANS IN RATS.

Oishi S, Morita M, Fukuda H
Tokyo Metropolitan Res. Lab. of Public Health, 24-1, Hyakunincho 3-chome, Shinjuku-ku, Tokyo, 160, Japan
Toxicol Appl Pharmacol; 43(1):13-22 1978

Male Sprague-Dawley-derived rats were fed either 100 ppm polychlorinated biphenyls (PCB) or 1 or 10 ppm polychlorinated dibenzofurans (PCDF), and the effects of these compounds evaluated. After 3 wk some of the rats on the 10 ppm PCDF diet showed some chloracne-like lesions on the ear. Absolute and relative wt of brain, and relative wt of liver and spleen were increased in rats fed PCB. Relative wt of liver, brain, lungs, spleen, adrenals, heart and testes were increased in rats fed 10 ppm PCDF, while absolute wt of heart and kidneys were significantly decreased. Cerebral edema was observed in all groups. In rats fed PCDF concentration, hematocrit, and mean corpuscular volume were significantly decreased. RBC counts of rats fed 10 ppm PCDF were significantly lower. Mean corpuscular concentrations were significantly higher in all treatment groups. In rats fed PCB, serum total protein, cholesterol, and serum cholinesterase activity were increased, and glucose, triglyceride and leucine aminopeptidase were decreased. In rats fed either PCDF diet, serum urea nitrogen, triglycerides, leucine aminopeptidase and glutamic-pyruvic transaminase were decreased, and cholesterol, serum glutamic-oxaloacetic transaminase and cholinesterase were increased. Total liver lipids were increased in all treatment groups. Testosterone concentrations in the testes were significantly decreased in rats fed 10 ppm PCDF. Urine sodium and potassium were normal. PCDF were more toxic than PCB, particularly on hematologic and thymic functions. (33 Refs)

33. TOXICOPATHOLOGY CHARACTERISTICS OF THE HALOGENATED AROMATICS (MEETING ABSTRACT).

McConnell EE
National Inst. Environmental Health Science, Research Triangle Park, NC
The Scientific Basis for the Public Control of Environmental Health Hazards, held by the New York Academy of Sciences in New York, 21-30 June, 1978. The New York Academy of Sciences, New York, New York, 1978.

The lethal dose of structurally related classes of aromatic hydrocarbons (dibenzodioxins, dibenzofurans, biphenyls and napthalenes) cause a similar clinical syndrome and pattern of lesions within the same animal species but cause different syndromes and lesions in different species. In addition, the clinicopathological syndrome differs somewhat between acute and chronic exposures. Liver lesions are conspicuous in mice and rats with these compounds but hepatic pathology is minimal in guinea pigs and non-human primates. In contrast, proliferative lesions of the urinary tract are found in the latter two species but not the former two. Cutaneous lesions are dramatic in primates but are rarely encountered in the other animal species. Thymic involution is the only lesion that is consistently observed in all species and with

both acute and chronic exposures. All the compounds studied to date are carcinogenic, particularly to the liver. (no Refs)

34. COMPARISON OF HYPERKERATOSIS INDUCED BY PCBS, PCDF AND PCDD APPLICATION.

Nishizumi M, Kuratsune M, Masuda Y

Dept. Public Health, Faculty Medicine, Kyushu Univ., Fukuoka, Japan

Fukuoka Acta Med; 66(10):600-604 1975

Polychlorinated biphenyls (PCBs) (Kanechlor 400, a commercial preparation), polychlorinated dibenzofuran (PCDF) (a mixture of tetra- and penta-chloro-dibenzofuran) or polychlorinated dibenzodioxin (PCDD) (2,3,7,8-tetrachloro-dibenzodioxin) was dissolved in acetone in different concentrations and applied on the inside of depilated rabbit's ear for 3 consecutive days. The redness on the skin was followed by thickening of the skin within 1 to 2 wk. Judging from the extent of hyperkeratosis induced by these three compounds, PCDD is approx 1,000 times stronger than PCBs or PCDF as an acnegen. (9 refs)

35. COMPARATIVE TOXICOLOGY OF CHLORINATED COMPOUNDS ON MAMMALIAN SPECIES.

Allen JR, Hargraves WA, Hsia MT, Lin FS

Dept. Pathology, Univ. Wisconsin Medical Sch., Madison, WI, 53706

Pharmacol Ther (Chemother); 7(3):513-547 1979

Chlorinated herbicides and insecticides as well as contaminants and additives that may be present in preparations of these compounds, are reviewed with regard to toxicity in humans and other mammals. The specific compounds discussed include 2,2-bis-(para-chlorophenyl)-1,1,1-trichloroethane (DDT), cyclodiene insecticides, chlorobenzenes, hexachlorocyclohexanes, chlorophenols, chlorophenoxyacetic acids, polychlorinated biphenyls (PCB), and 2,3,7,8-tetrachlorodibenzo-para-dioxin (TCDD). Toxicity of these compounds in humans is discussed with respect to cases of accidental poisoning and occupational exposure. Toxicity of these compounds in experimental animals is discussed with respect to general, CNS, reproductive, liver and kidney, and immunological effects, as well as carcinogenicity, mutagenicity, and teratogenicity. Unique aspects of certain compounds are examined, including the following: the relationship between chlorine content and toxicity for chlorobenzenes; absorption, accumulation, and elimination of hexachlorobenzene; possible mechanisms of toxic action of hexachlorobenzene and hexachlorocyclohexanes; and molecular alterations associated with the toxicity of chlorophenoxyacetic acids, PCB, and TCDD. (337 Refs)

36. TOXICITY OF 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN IN THE GOLDEN SYRIAN HAMSTER.

Olson JR, Holscher MA, Neal RA

Center in Toxicology, Vanderbilt University, Nashville, Tennessee 37232

Toxicol Appl Pharmacol; 55:67-78 1980

37. THE EFFECT OF TOTAL PARENTERAL NUTRITION ON THE TOXICITY OF 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN IN THE RAT.

Gasiewicz TA, Holscher MA, Neal RA

Center in Toxicology, Department of Biochemistry, Vanderbilt University School of Medicine, Nashville, Tennessee 37232

Toxicol Appl Pharmacol; 54:469-488 1980

38. EFFECTS OF ENVIRONMENTAL CONTAMINANTS ON THE IMMUNE SYSTEM.

Koller LD

Veterinary Medicine, Univ. Idaho, Moscow, ID

Adv Vet Sci Comp Med; 23:267-295 1979

Environmental contaminants that alter the immune response in animals are reviewed with emphasis on those that are effective at subclinical dosages after prolonged exposure. Methods of detecting altered immune function are outlined and include gross and histopathologic examination of lymphoid tissue, immunological challenge, immunoassays for examination of humoral immunity, macrophage studies, and studies of cell-mediated immunity, such as delayed hypersensitivity, graft-versus-host reactions, and antibody-dependent cell-mediated cytotoxicity. Early data suggesting that environmental pollutants may interfere with the immune response of a host are reviewed. Studies dealing with the effects of specific agents on the immune system of experimental animals are described; six tables are presented to compare different experiments using the same agents in terms of species studied, parameter measured, and result produced. Heavy metals that have been studied include lead, cadmium, and mercury; the effects of selenium, arsenicals, cobalt, nickel, carbon, silica, chromium, and platinum on the immune system have also been investigated. Industrial chemicals, such as polychlorinated biphenyls and tetrachlorodibenzo-para-dioxin, and many pesticides that have been studied are discussed; the effects of dichlorodiphenyltrichloroethane (DDT) on the immune response are described in detail. (114 Refs)

39. LABORATORY STUDIES ON THE IMMUNE EFFECTS OF HALOGENATED AROMATICS.

Luster MI, Faith RE, Clark G

Environmental Biology and Chemistry Branch; National Institute of Environmental Health Sciences; Research Triangle Park, N.C. 27709

Ann NY Acad Sci; 320:473-484 1979

40. INVESTIGATIONS ON THE EFFECTS OF 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN (TCDD) ON PARAMETERS OF VARIOUS IMMUNE FUNCTIONS.

Faith RE, Luster MI

Environmental Biology and Chemistry Branch, National Institute of Environmental Health Sciences; Research Triangle Park, N.C. 27709

Ann NY Acad Sci; 320:564-571 1979

B.

Modification of Toxicologic Effects Induced by Dioxins and Dibenzofurans to Experimental Animals

41. QUANTITATIVE AND QUALITATIVE CHANGES IN THE METABOLISM OF BENZO(A)PYRENE IN RAT TISSUES AFTER INTRAGASTRIC ADMINISTRATION OF TCDD.

Uotila P, Parkki MG, Aitio A
Dept. Physiology, Univ. Turku, SF-20520 Turku 52, Finland
Toxicol Appl Pharmacol; 46(3):671-683 1978

The effect of pretreatment with 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD, 20 ug/kg given intragastrically 1 wk before sacrifice) on the in vitro metabolism of benzo(a)pyrene (BP) by liver, lung, and kidney preparations from Wistar and Gunn (deficient in glucuronide conjugation) rats was studied. TCDD greatly increased the metabolism of BP to ethyl acetate-soluble metabolites by liver homogenates and microsomes. The increase was greatest in the case of unidentified 'near origin' metabolites. 4,5-Dihydrodiol was the major metabolite formed by control liver preparations, whereas the 9,10-and 7,8-dihydrodiols were the major metabolites formed after TCDD treatment. TCDD pretreatment also drastically increased the metabolism of BP to water-soluble metabolites and significantly increased the liver microsomal protein content in Wistar, but not Gunn, rats. The increase in the amounts of phenols and quinones after TCDD treatment was much less pronounced. TCDD greatly increased the metabolism of BP to dihydrodiols, phenols, and unidentified metabolites by kidney and lung microsomes; the increase was greater with kidney microsomes from Gunn rats than with those from Wistar rats. TCDD treatment decreased the protein content of the kidney, and it had no effect on the metabolism of BP to water-soluble metabolites by kidney microsomes. The amount of BP metabolites covalently bound to liver, but not kidney or lung, microsomes was increased by TCDD pretreatment. (35 Refs)

42. EFFECTS OF POLYHALOGENATED AROMATIC HYDROCARBONS ON BENZO(A)PYRENE HYDROXYLASE ACTIVITY IN THE INTESTINE AND LIVER.

Manis J, Kim G
Div. Gastroenterology, Dept. Medicine, State Univ. New York, Downstate Medical Center, Brooklyn, NY, 11203
Lif Sci; 26(17):1431-1439 1980

Aryl hydrocarbon hydroxylase (AHH) has been measured as benzo(a)pyrene hydroxylase in the intestine and liver of rats and mice treated with a single dose of different polyhalogenated aromatic hydrocarbons. Max stimulation of liver AHH activity is reached with a dose of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) half as great as that necessary for max stimulation of the intestine. The duration of the effect of TCDD on intestinal AHH differs from the constant increase that occurs in the liver. Although the magnitude of the stimulation by 1,1,1-trichloro-2,2-bis(p-chlorophenyl)ethane (DDT) is less than that of TCDD, the qualitative changes in intestinal and liver AHH are similar. The changes in activity of intestinal and hepatic AHH were not directly correlated in the tissues of rats treated with several other polyhalogenated aromatic hydrocarbons. Liver and intestinal AHH activity were affected differently by fasting. These results suggest that AHH activity in the intestine and liver have different control mechanisms. (Author abstract) (15 Refs)

C.
Induction of Mixed Function Oxidases by Dioxins and Dibenzofurans to Experimental Animals

43. RESOLUTION OF TWO FORMS OF CYTOCHROME P-450 FROM LIVER MICROSOMES OF RABBITS TREATED WITH 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN.

Johnson EF, Muller-Eberhard U
Dept. Biochemistry, Scripps Clinic and Res. Foundation, La Jolla, CA 92037
J Biol Chem; 252(9):2839-2845 1977

Chromatography of male New Zealand rabbit liver microsomal preparations from animals treated 5 days previously with 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD: 94 nanomoles ip) resulted in the isolation of two forms of cytochrome P-450. The yield of the major form (P-450c) was approx three times that of the minor one (P-450ab). The reduced CO difference spectra and the n-octylamine difference spectra for these two forms were different; the spectra for P-450c corresponded to those from TCDD-treated animals, but the spectra for P-450ab corresponded to those of untreated animals. Electrophoresis of P-450c showed a single band with an Mr of 54,000; the minor form contained several peptides with an Mr of 60,000 and 47,000. Antibody produced against P-450c inhibited microsomal acetanilide hydroxylation by 80%, but it did not cross-react with P-450ab. Furthermore, it did not inhibit the hydroxylation of 3,4-benzpyrene or coumarin, the N-demethylation of aminopyrine, or the O-deethylation of 7-ethoxycoumarin catalyzed by rabbit liver microsomes. It is concluded that at least two forms of cytochrome P-450 exist in rabbit liver microsomes following TCDD treatment and that they differ in immunological properties and catalyze different monooxygenase activities. (30 Refs)

44. 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN INDUCTION OF ARYL HYDROCARBON HYDROXYLASE IN FEMALE RAT LIVER. EVIDENCE FOR DE NOVO SYNTHESIS OF CYTOCHROME P-448.

Kitchin KT, Woods JS
Lab. Environmental Toxicology, Natl. Inst. Environmental Health Sciences, NIH, P. O. Box 12233, Research Triangle Park, NC, 27790
Mol Pharmacol; 14(5):890-899 1978

The mechanism of 2,3,7,8-tetrachlorobenzo-p-dioxin (TCDD)-induced increases in microsomal cytochrome P-448 and aryl hydrocarbon hydroxylase (AHH) activity in female Sprague-Dawley rat liver was investigated. The rats were given either corn oil or TCDD (2 ug/kg, po), and sacrificed after 1, 3, 7 or 28 days. Their hepatic delta-aminolevulinic acid synthetase, cytochrome P-450, aminopyrine N-demethylase and aryl hydrocarbon hydroxylase levels were determined. The time course of TCDD induction of AHH in female rat liver was investigated by administration of TCDD, ip at zero time then determining hepatic microsomal AHH activity at 4, 6, 9, 12, 18 and 24 hr after treatment. No increase in the activity of delta-aminolevulinic acid synthetase was observed, while a 23-fold increase in the level of cytochrome P-448-mediated AHH was observed 24 hr after TCDD treatment. The induction of new cytochrome P-448 was completely prevented by actinomycin D and cycloheximide, but not $CoCl_2$, while an increase in AHH activity by TCDD was observed. The addition of heme to whole liver homogenates from rats given TCDD and $CoCl_2$ caused an in vitro reconstitution of cytochrome P-450 and increases in enzymatically active AHH levels. Thus, TCDD may induce de novo protein synthesis of apocytochrome P-448, which combines with heme to yield new cytochrome P-448 and a concomitant increase in AHH activity. TCDD selectively induces the formation of cytochrome P-448, leading to increased AHH activity. Protein

synthesis, rather than heme synthesis, is the rate-limiting event in this process. (54 Refs)

45. IDENTIFICATION OF THE MAJOR CYTOCHROME P-450 FORM TRANSPLACENTALLY INDUCED IN NEONATAL RABBITS BY 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN.

Norman RL, Johnson EF, Muller-Eberhard U
Dept. Biochemistry, Scripps Clinic and Res. Foundation, La Jolla, CA, 92037
J Biol Chem; 253(23):8640-8647 1978

Transplacental induction of cytochrome P-450 by 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) was studied in newborn rabbit liver. This treatment increased a single cytochrome species in microsomes of newborn rabbit liver as demonstrated by sodium dodecyl sulfate-polyacrylamide gel electrophoresis. This cytochrome species had the same mobility as cytochrome P-450 form 6, isolated from liver microsomes of TCDD-treated adult rabbits. The identity of the major component was confirmed by a comparison of its peptide fingerprint with that of purified adult form 6. This assignment was further supported by immunological studies which showed that monospecific antibody developed against adult form 6 reacted with microsomes from TCDD-treated newborns but not with the microsomes from control newborns. Benzo(a)pyrene hydroxylase and 7-ethoxyresorufin O-deethylase activities are associated with purified form 6 reconstituted with purified reductase and phospholipid. TCDD treatment increased these enzyme activities in newborn microsomes. Furthermore, these enzyme activities were strongly inhibited by alpha-naphthaflavone both in the reconstituted system and in microsomes from TCDD-treated newborns. These results demonstrate that microsomal metabolism in TCDD-treated newborn rabbits reflects the catalytic properties of the predominant cytochrome P-450 species, which is form 6. In the adult rabbit, two forms of cytochrome P-450 are induced by TCDD, form 4 which is the major species induced by TCDD and form 6. This difference in the response of adult and neonatal rabbits to TCDD suggests that an age-dependent factor(s) controls the induction of form 4. Variations in cytochrome composition with development and in response to inducers will affect xenobiotic metabolism and may have important consequences on the susceptibility of an animal to chemical carcinogenesis. (Author abstract) (45 Refs)

46. THE ROLE OF CYTOCHROME P-450 FORMS IN 2-AMINOANTHRACENE AND BENZO[ALPHA]PYRENE MUTAGENESIS (MEETING ABSTRACT).

Norman RL, Muller-Eberhard U, Johnson EF
Scripps Clinic and Res. Foundation, La Jolla, CA, 92037
Fed Proc; 38(3,part1):535 1979

The metabolic activation of two suspected carcinogens, the arylamine, 2-aminoanthracene, and the polycyclic aromatic hydrocarbon, benzo(a)pyrene, by three forms of purified rabbit liver cytochrome P-450 was investigated. One form, form 6, is induced by 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) in the livers of newborn rabbits. In addition to form 6, a second form, form 4, is induced by TCDD in adult rabbit liver. The third form, form 2, is the principal phenobarbital-induced species in both newborn and adult rabbit livers. Each of these forms was reconstituted with purified NADPH-dependent reductase and lecithin. Production of mutagenic metabolites from either 2-amimoanthracene or benzo(a)pyrene by each cytochrome P-450 form was detected by counting the number of back mutations to histidine independence of the Salmonella typhimurium tester strain TA 98. Mutagenesis by 2-aminoanthracene was catalyzed predominantly by form 4 while form 6 was the most active of the three forms in the metabolism of benzo(a)pyrene to mutagenic products. These findings suggest that specific forms of cytochrome P-450 activate particular carcinogens. (no Refs)

47. DEPRESSION OF GUINEA-PIG TESTICULAR MICROSOMAL CYTOCHROME P-450 CONTENT BY 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN (TCDD) (MEETING ABSTRACT).

Peters PG, Tofilon PJ, Piper WN
Dept. Pharmacology, Univ. California, San Francisco, CA, 94243
Pharmacologist; 21(3):211 1979

Adverse effects in man associated with 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) include hirsutism and chloracne, which prompted us to investigate the effects of this substance on the regulation of guinea pig testicular cytochrome P-450. Microsomal heme, cytochromes P-450 and b5 and delta-aminolevulinic acid synthetase (ALAS) activity were assayed following administration of a single dose of TCDD (po; 1 ug/kg). Animals were sacrificed at 3, 6 or 9 days. At day 3, there were no significant changes in ALAS activity, cytochrome P-450 or heme contents. At day 6, there was a marked fall in the cytochrome P-450 content (59%) and a decrease in the heme content (24%). There were no changes in ALAS activity or microsomal cytochrome b5 content. At day 9, the level of cytochrome P-450 was still decreased (41%) but there was no significant difference between the microsomal heme content of control and TCDD treated guinea pigs. These results indicate that TCDD administration depresses guinea pig testicular microsomal heme and cytochrome P-450 content. Since cytochrome P-450 is known to mediate testicular steroid hydroxylations, it is probable that TCDD interferes with steroidogenesis in this organ. (no Refs)

48. MULTIPLE FORMS OF CYTOCHROME P-450 FROM LIVER MICROSOMES OF RABBITS TREATED WITH 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN (MEETING ABSTRACT).

Johnson EF, Muller-Eberhard U
Scripps Clinic and Res Foundation, La Jolla, Ca 92037
Fed Proc; 36(3):833 1977

Three forms of cytochrome P-450, designated a, b, and c were isolated with specific contents of 9.7, 12.0 and 17.8 nmoles cytochrome P-450 per mg protein. Molecular weights estimated by polyacrylamide gel electrophoresis in the presence of sodium dodecyl sulfate were 60,000 for the b and 54,500 for the c form. The a fraction consists of several peptides, the most prominent corresponds to a molecular weight of 48,000. The presence of high spin ferric heme is suggested by the absorption spectrum of oxidized cytochrome P-450c. Forms a and b display spectra typical of low spin ferric heme. Antibodies developed against forms b or c show no immunological cross-reactivity with the other forms. Benzo(a)pyrene activity is catalyzed primarily by the b form and acetanilide hydroxylation by the c form. Both cytochromes are equally active in the 0-deethylation of 7-ethoxyresorufin but exhibit low activity with benzphetamine as a substrate. Thus, there appear to be at least three discrete forms of cytochrome P-450 in rabbit liver microsomes following 2,3,7,8-tetrachlorodibenzo-p-dioxin treatment. (Author Abstract)

49. CARCINOGEN INDUCTION OF CYTOCHROME-P448-ASSOCIATED ENZYMES: DETECTION BY IN VIVO BREATH ANALYSIS (MEETING ABSTRACT).

Hepner GW, Piken E
Dept. Medicine, Univ. California Los Angeles/Harbor General Hosp., Torrance, CA
Clin Res; 26(3):498A 1978

Many carcinogens induce the production of an abnormal hemoprotein, cytochrome P-448. We therefore synthesized [C14] dimethylaminoazobenzene, ([C14] DMAB), a substrate of cytochrome P-448-associated enzymes, and used an in vivo breath analysis technique to determine its rate of N-demethylation as a non-invasive means of assessing exposure to carcinogens. Rats were treated with 1 of 3 carcinogens: 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), 3-methylcholanthrene (3MC) or Aroclor. TCDD and 3MC are inducers of cytochrome P-448; Aroclor induces both cytochrome P-448 and cytochrome P-450. In addition, studies were performed with rats treated with phenobarbital, an inducer of cytochrome P-450 but not cytochrome P-448. C1402 half-life after administration of [C14] DMAB was 38.5 +- 5.5 min in control rats, and significantly shorter (p less than 0.001) in rats treated with TCDD (28.9 +- 5.0 min), 3MC (27 +- 2.6 min) or Aroclor (29.2 +- 5.8 min); it was unaffected by treatment with phenobarbital (34.0 +- 4.5 min). Studies with [C14] aminopyrine, a substrate for cytochrome P-450-associated enzymes, showed that the half-life of breath C1402 was significantly (p less than 0.001) decreased in Aroclor- and phenobarbital-treated rats, but unchanged in the TCDD- and 3MC-treated rats, indicating that cytochrome P-450 had been induced by Aroclor and phenobarbital but not by TCDD or 3MC. We conclude that carcinogen induction of cytochrome P-448 can be determined in vivo by a simple C1402 breath analysis technique after administration of [C14] DMAB.

50. 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN (TCDD) INDUCED SYNTHESIS OF CYTOCHROME P-448 AND ARYL HYDROCARBON HYDROXYLASE (AHH) ACTIVITY IN FEMALE RAT LIVER (MEETING ABSTRACT).

Kitchin KT, Woods JS
Natl. Inst. Environmental Health Science, NIH, Res. Triangle Park, NC 27709
Pharmacologist; 19(2):232 1977

These studies investigated the mechanism of induction of cytochrome P-448 and aryl hydrocarbon hydroxylase (AHH) by 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), a potent hepatotoxin in mammals. TCDD (2 microg/kg, po) produced 23, 37, 45 and 13-fold increases in levels of cytochrome P-448 mediated AHH in hepatic microsomes of female rats 1, 3, 7 and 28 days after treatment. In contrast, no changes in levels of delta-amino-levulinic acid synthetase, the rate limiting enzyme in heme biosynthesis, or in cytochrome P-450-mediated aminopyrine-N-demethylase were observed. Concurrent administration of either cycloheximide (2 mg/kg, ip), an inhibitor of cytoribosomal protein synthesis, or CoCl2 (60 mg/kg, sc), a heme depletor, reduced the induction of AHH by TCDD by 64 and 29% respectively. In vitro studies showed that 600% greater reconstitution of total microsomal apocytochromes with hemin and 450% greater increase in AHH levels occurred in homogenates of CoCl2 and TCDD treated rats as compared to controls. These studies indicate that TCDD induces the synthesis of apocytochrome P-448 which combines with heme to form new cytochrome P-448 and thus increases AHH activity. (no Refs)

51. EVIDENCE IN RAT AND MOUSE LIVER FOR TEMPORAL CONTROL OF TWO FORMS OF CYTOCHROME P-450 INDUCIBLE BY 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN.

Guenthner TM, Nebert DW
Developmental Pharmacology Branch, Natl. Inst. Child Health and Human Development, NIH, 9000 Rockville Pike, Bethesda, MD, 20014
Eur J Biochem; 91(2):449-456 1978

In the liver of perinatal rats or mice, the ratio of 2,3,7,8-tetrachlorodibenzo-p-dioxin-induced aryl hydrocarbon hydroxylase to total cytochrome P-450 content decreases, whereas the ratio of 2,3,7,8-tetrachlorodibenzo-p-dioxin-induced acetanilide 4-hydroxylase to total cytochrome P-450 content increases, between 18 or 19 days and 22 days following conception. The ontogenesis of inducible aryl hydrocarbon hydroxylase corresponds well with increases in a 56,000 mol wt electrophoretic band; we suggest this band represents the cytochrome P(1)-450 subunit (cytochrome P(1)-450 refers to a polycyclic aromatic-inducible form of cytochrome P-450 associated with induced aryl hydrocarbon hydroxylase activity). The later temporal expression of inducible acetanilide 4-hydroxylase closely parallels 2,3,7,8-tetrachlorodibenzo-p-dioxin-induced increases in size of a 54,000 mol wt electrophoretic band and a 2-3 nanometer hypochromic shift in the Soret peak of the total microsomal reduced cytochrome P-450-CO complex. We suggest this band represents the cytochrome P-448 subunit. Previous work from this laboratory has shown that this developmental difference is separated by several wk in rabbit liver, as compared with several day's separation shown in this report with rat or mouse liver. The data here therefore provide evidence in the rodent for temporal control of the expression of different structural gene products regulated by the Ah locus. (Author abstract) (41 Refs)

52. COMPARATIVE INDUCTION OF INTESTINAL MIXED-FUNCTION OXIDASE ACTIVITIES BY VARIOUS POLYCYCLIC HYDROCARBONS (MEETING ABSTRACT).

Hassing JM, Stohs SJ
Univ. Nebraska Medical Center, Omaha, NB, 68105
Fed Proc; 38(3,part1):365 1979

The effects of 3-methylcholanthrene (MC), benz(a)anthracene (BA), 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) and Arochlor-1254 on the induction of microsomal mixed-function oxidase activity in rat intestinal mucosa were compared. Eighteen hr after intragastric administration of the inducing agent, intestinal mucosal microsomes were prepared and the activities of 7-ethoxyresorufin (ER) deethylase and benzo(a)pyrene (BP) monooxygenase determined. MC demonstrated the greatest inductive potency in intestinal microsomes of the agents tested, stimulating ER deethylase activity 10-fold over control activity, and BP monooxygenase activity 30-fold. TCDD administration resulted in a 10-fold stimulation of BP monooxygenase activity over control levels. BA was the least potent inducer, producing a 70% stimulation of ER deethylase activity. Intestinal mixed-function oxidases are highly susceptible to induction by polycyclic hydrocarbons. Dramatic and selective increases in activity are observed within 18 hr after oral administration of these agents. (no Refs)

53. INDUCTION OF DRUG METABOLIZING ENZYMES IN DIFFERENT RAT TISSUES BY TCDD.

Parkki MG, Aitio A
Dept. Physiology, Univ. Turku, Kiinamyllynkatu 10, SF-20520 Turku 52, Finland

Arch Toxicol (Berl); (1):261-265 1978

The effects of TCDD (2,3,7,8-tetrachlorodibenzo-p-dioxin) were studied on drug metabolizing enzymes in different rat tissues. Benzpyrene hydroxylase measured with the fluorometric method (3- and 9-hydroxylation) enhanced in liver 3-fold, in kidney 60-fold and in lung 7-fold. Measured with the radiometric method, which measures the total metabolism of benzpyrene, the activity of aryl hydrocarbon hydroxylase increased in liver 5-fold and in kidney 14-fold. This indicates, that the share of 3- and 9-hydroxylation compared to the total hydroxylation of benzpyrene decreased in liver but increased in kidney. Ethoxycoumarin deethylase enhanced in liver 5-fold, in kidney 23-fold and in lung 5-fold. The content of cytochrome P-450 doubled in liver and kidney. Uridine diphosphate glucuronosyltransferase activity (4-methylumbelliferone) increased 7-fold in liver measured in untreated microsomes. Treatment of microsomes with digitonin, trypsin or phospholipase A revealed latency both in control and TCDD induced microsomes but were not able to uncover any additional induction. In kidney and lung only minor increase in activity was detected. The activities of epoxide hydrase, glutathione S-transferase, the total glycine conjugation pathway and glycine N-acyltransferase were not altered clearly in any tissue studied. No enzymes were enhanced in intestine or testis. The present data indicate that the inducing ability of TCDD is strictly tissue and enzyme dependent. (Author abstract) (5 Refs)

54. ACTIVATION OF NITROSAMINES TO MUTAGENS BY POSTMITOCHONDRIAL FRACTION OF HAMSTER PANCREAS.

Scarpelli DG, Rao MS, Subbarao V, Beversluis M, Gurka DP, Hollenberg PF
Dept. Pathology, Northwestern Univ. Medical Sch., Chicago, IL, 60611

Cancer Res; 40(1):67-74 1980

The nitrosamines 2,6-dimethylnitrosomorpholine (DMNM) and N-nitrosobis(2-oxopropyl)amine (NBOP) are carcinogens which induce adenocarcinoma of the pancreatic ducts in the Syrian golden hamster. Since both compounds are indirect carcinogens and must be metabolically activated to their carcinogenic form(s) by the enzyme system(s) of the host, the capacity of the mixed-function oxidases in hamster pancreas 9,000 x gravity (S9) fraction to activate these compounds to mutagens was studied. The postmitochondrial fraction (S-9) prepared from pancreas was capable of converting both compounds to forms mutagenic for Salmonella typhimurium TA 1535. The mutagenic activity of DMNM with hamster pancreas S-9 was dose dependent, with 22 +-7 (standard error) revertants formed per mg protein of S-9 with 1 mg DMNM and 109 +-9 revertants formed per mg with 10 mg DMNM. Although NBOP is the more potent carcinogen, it was consistently less mutagenic, with 12 +-4 revertants being formed per mg of S-9 protein with 1 mg of NBOP and 39 +-8 revertants formed when 10 mg of carcinogen were used. The capacity of the hamster pancreatic S-9 to convert both carcinogens to mutagens was increased significantly following pretreatment of the hamster with a single dose of beta-naphthoflavone (140 +-12/10 mg DMNM), or 2,3,7,8-tetrachlorodibenzo-p-dioxin (182 +-11/10 mg DMNM). A concomitant increase in the aryl hydrocarbon hydroxylase activity of pancreas S-9 isolated from hamsters treated with beta-naphthoflavone (4 x control) or 2,3,7,8-tetrachlorodibenzo-p-dioxin (15 x control) was observed, suggesting a relationship between the levels of aryl hydrocarbon hydroxylase activity and the metabolic activation of DMNM and NBOP in the pancreas. In contrast to 2,3,7,8-tetrachlorodibenzo-p-dioxin and beta-naphthoflavone, 3-methylcholanthrene induction did not result in an increased capacity of the S-9 to activate either DMNM or NBOP to mutagenic metabolites. This suggests that a different form of the enzyme may be induced by 3-methylcholanthrene and that it metabolizes DMNM by predominantly detoxification pathways leading largely to noncarcinogenic metabolites. The absolute requirement by these pancreatic enzymes for reduced nicotinamide adenine dinucleotide phosphate, and their inhibition by alpha-naphthoflavone and 2,5-diphenyloxazole are strong points of evidence that they are mixed-function oxidases. (Author abstract) (39 Refs)

55. RELATIONSHIP BETWEEN LEVELS OF ARYL HYDROCARBON HYDROXYLASE ACTIVITY AND SUSCEPTIBILITY TO 3-METHYLCHOLANTHRENE AND BENZO[A]PYRENE-INDUCED CANCERS IN INBRED STRAINS OF MICE.

Kouri RE

Carcinogenesis - A Comprehensive Survey. Freudenthal R, Jones PW, ed. New York, Raven Press, vol. 1, 1976.

An investigation was made of the relationship between aryl hydrocarbon hydroxylase (AHH) activity in crosses of various inbred mouse strains [3H/fCum (C3), C57Bl/6Cum (B6), DBA/2Cum (D2), and AKR/J] and their susceptibility to carcinogenesis by 3-methylcholanthrene (3-MC) and benzo(a)pyrene (BP). In crosses in which the level of AHH inducibility segregates as a single codominant gene (i.e., C3D2F1), or where noninducibility is dominant, the frequency of fibrosarcomas 3-MC directly correlates to the expression of hepatic AHH. Susceptibility to BP is also correlated with high levels of AHH inducibility. A similar correlation was observed in the lung between AHH responsiveness and the tumorigenic effect elicited by the intratracheal instillation of 3-MC in B6, D2, B6D2, (F1), F1 x B6, and F1 x D2 mice (in crosses involving B6 and D2 mice AHH responsiveness segregates as an autosomal dominant gene). In F1 x D2 mice with noninducible pulmonary AHH, 25% developed lung lesions after administration of 3-MC (500 microg/wk for 4 wk); mice in F1 x D2 mice with inducible AHH, 75% developed such lesions. A study was made of the effects of treatment with the potent AHH inducer, 2,3,7,8-tetrachlorodibenzo(a)dioxin (TCDD), on 3-MC-induced sc tumors in D2 mice. TCDD is capable of inducing hepatic AHH levels even in "nonresponsive" D2 mice. Coadministration of TCDD (1 microg) with 3-MC (150 microg) brought about a five-to sixfold increase in tumor incidence. The same dose of TCDD administered 48 hr prior to 3-MC had little effect on the numbers of tumors induced; since the highest specific activity of AHH occurred 48 hr after TCDD treatment, other factors apart from elevated AHH levels are involved in enhancement of tumor susceptibility. (34 refs)

56. TIME COURSE OF THE INDUCTION OF ARYL HYDROCARBON HYDROXYLASE IN RAT LIVER NUCLEI AND MICROSOMES BY PHENOBARBITAL, 3-METHYLCHOLANTHRENE, 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN, DIELDRIN AND OTHER INDUCERS.

Viviani A, Lutz WK, Schlatter C

Inst. Toxicology, Federal Inst. Technology, CH-8603 Scherzenbach, Switzerland

Biochem Pharmacol; 27(17):2103-2108 1978

The time course of the induction of aryl hydrocarbon hydroxylase (AHH) was measured in male liver nuclei and microsomes after treatment of adult animals (Sprague-Dawley-derived SIV 50 strain) with various inducers for up to 14 days. After daily ip injection of 3-methylcholanthrene (MC, 20 mg/kg), the nuclear activity increased to a max of 600% of the control activity after 4 days, whereas the microsomal activity was 400% of the control activity at the same date. After 12 days, both activities equilibrated at 400%. A similar time course was found after a single ip injection of 2,3,7,8-tetrachloro-dibenzo-p-dioxin (0.01 mg/kg) with an induction of 500% and 300% for nuclei and microsomes, respectively, after 2 days, and to 400% for both after 12 days. Phenobarbital (PB) was given continuously in the drinking water (1 g/liter); it induced microsomal activity to 200% after 8 days and 170% after 14 days. The nuclear activity was only slightly induced to a constant level of 130% between days 8 and 14. Dieldrin did not significantly increase the microsomal activity after daily ip injection (20 mg/kg), but the nuclear activity was raised to 200% after 3 days, and lowered to control values after 12 days. Other inducers tested were benz[a]anthracene (BA), hexachlorobenzene (HCB), and 1,1,1-trichloro-2,2-bis(p-chlorophenyl)ethane (DDT). The induction pattern with BA was similar to that of MC, a model compound for the group of cytochrome P-448 inducers. The induction by HCB and DDT resembled that by PB, a typical cytochrome P-450 inducer. The results indicate that long-term treatment results in an equal relative induction of AHH activity in microsomes and nuclei and that only the absolute value of the induction is dependent on the inducer used. (29 Refs)

57. COMPARISON OF INDUCTION PATTERNS OF RAT HEPATIC MICROSOMAL MIXED-FUNCTION OXIDASES BY PESTICIDES AND RELATED CHEMICALS.

Madhukar BV, Matsumura F

Pesticide Res. Center, Michigan State Univ., East Lansing, MI, 48824

Pestic Biochem Physiol; 11(1-3):301-308 1979

Pesticides and related compounds were categorized according to their cytochrome P-450 induction patterns in rat hepatic microsomes. Tetrachlorodibenzo-p-dioxin and a polychlorinated biphenyl induced different types of cytochrome from the rest of the cytochrome P-450 inducers, as judged by the drastic change in the 455:430-nanometer ratio. When six different drugs were used as substrates to recognize differences among induction patterns of mixed-function oxidase activities, four basic groups of inducers were recognized. Phenobarbital-, DDT- chlordane-, mirex-, and kepone-induced liver microsomes were similar in the drug metabolizing activity. Qualitative changes in drug-metabolizing enzyme activities after treatment with pesticides appear to be group-specific. (20 Refs)

58. GENETIC EXPRESSION OF MICROSOMAL ELECTRON TRANSPORT ASSOCIATED WITH ARYL HYDROCARBON HYDROXYLASE INDUCTION IN MICE.

Blumer JL

Northwestern Univ., Evanston, IL

Diss Abstr Int [B]; 38(12):5874B 1978

The specific aims of this project were: (1) to characterize as completely as possible the hepatic microsomal electron transport systems in constitutive C57BL/6J and DBA/2J mouse microsomes. (2) to evaluate any differences in microsomal electron transport phenomena in the constitutive microsomes of the two strains of mice with respect to the known genetic difference between them with respect to aromatic hydrocarbon responsiveness. (3) to describe and evaluate the effects of the inducing agents phenobarbital, 3-methylcholanthrene and 2,3,7,8-tetrachloradibenzo-p-dioxin on the electron transport parameters evaluated in microsomes from constitutive C57BL/6J and DBA/2J mice. (4) to use the alterations in microsomal electron transport reactions associated with aryl hydrocarbon hydroxylase (AHH)-induction to provide some insight into the mechanism of microsomal drug oxidations. Results from studies suggest that there exists a strain difference in the juxtaposition or mutual orientation of the components of the microsomal electron transport systems in the two inbred strains of mice. The genetic regulation of this strain difference appears to be under the control of the Ah locus. Agents which induce microsomal AHH activity in responsive mice appear to alter these electron transport interactions in both strains. This suggests that AHH induction may be a two event process in which the first involves a change in microsomal architecture and the second involves a change in the predominant form of P450 present.

59. MULTIPLICITY OF INDUCTION PATTERNS OF RAT LIVER MICROSOMAL MONO-OXYGENASES AND OTHER POLYPEPTIDES PRODUCED BY ADMINISTRATION OF VARIOUS XENOBIOTICS.

Sharma RN, Cameron RG, Farber E, Griffin MJ, Joly JG, Murray RK

Dept. Biochemistry, Univ. Toronto, Toronto, Ontario, Canada M5S 1A8

Biochem J; 182(2):317-327 1979

Induction of hepatic microsomal mono-oxygenase species after administration of various xenobiotics is a well-documented phenomenon. To examine the number and specific species of rat liver microsomal membrane polypeptides involved in such responses, we have used sodium dodecyl sulfate/polyacrylamide-gel electrophoresis to analyse microsomal fractions from animals treated with a number of important xenobiotics. The following are the principal points to have emerged from this study. (1) A minimum of 12 electrophoretically distinct patterns of induction of hemopolypeptides and other polypeptides could be distinguished after administration, either singly or in certain combinations, of phenobarbital, 3-methylcholanthrene, polychlorinated biphenyls, 2-acetylaminofluorene, safrole (or isosafrole), pregnenolone-16alpha-carbonitrile and ethanol. The patterns consisted of various permutations of the amounts of eight polypeptides of 47,000-56,000 mol wt, of which at least three were hemopolypeptides. The possible identities of these polypeptides, which included species of cytochrome P-450, cytochrome P-448 and epoxide hydratase, are discussed. (2) Agents (3-methylcholanthrene, benzo[a]-pyrene, polychlorinated biphenyls, 2,3,7,8-tetrachlorodibenzo-p-dioxin and beta-naphthoflavone) that result in the induction of cytochrome P-448 caused a marked increase in two polypeptides of 54,000 and 56,000 mol wt, whereas safrole and

isosafrole induced only the former polypeptide. (3) Administration of 2-acetylaminofluorene resulted in the induction of two polypeptides; evidence is presented that suggests that one of these is a species of epoxide hydratase and that the other may be a novel hemopolypeptide. (4) The overall results emphasize the complexity of the responses exhibited by rat liver microsomal fractions to the administration of xenobiotics. (Author abstract) (29 Refs)

60. GENETIC DIFFERENCES IN THE AROMATIC HYDROCARBON-INDUCIBLE N-HYDROXYLATION OF 2-ACETYLAMINOFLUORENE AND ACETAMINOPHEN-PRODUCED HEPATOTOXICITY IN MICE.

Thorgeirsson SS, Felton JS, Nebert DW
Natl. Inst. Child Health Hum. Dev., Bethesda, Md.
Mol Pharmacol; 11(2):159-165 1975

Genetically different C57BL/6N (B6) and DBA/2N (D2) inbred mice were given microsomal enzyme inducers 3-methylcholanthrene (MC), beta-naphthoflavone (BNF), 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), and sodium phenobarbital (PB) to study their effect on genetic differences in N-hydroxylation of 2-acetylaminofluorene (2-AAF) and acetaminophen. Each mouse was given MC or BNF, 80 mg/kg, 48 hr prior to sacrifice. PB-treated mice received the drug ip for three days, and were sacrificed 24 hr after the last injection. TCDD-treated mice were given 100 microg/kg 48 hr prior to assay. Hydroxylase activity in the liver was then determined. The results showed an increase in the N-hydroxylation of 2-AFF following MC treatment that appeared to segregate as a single autosomal dominant gene in reciprocal matings between B6 and D2 inbred mice, and that the N-hydroxylase induction was always associated with induction of aryl hydrocarbon hydroxylase activity by MC. There was a high correlation between the hydroxylase and N-hydroxylase activities in the livers of B6 and B2 mice treated with inducers MC, BNF, TCDD, and PB. There was a striking correlation not only with the presence or absence of induction, but also with its magnitude. Prior treatment with MC potentiated both the incidence and severity of acetaminophen-induced hepatic necrosis in B6 mice, but had little effect on D2 mice. The extent of hepatotoxicity caused by acetaminophen administered ip to these two strains of mice was also highly associated with both aromatic hydrocarbon inducible monooxygenase 'activities': aryl hydrocarbon hydroxylase and acetylarylamine N-hydroxylase. It is suggested that cytochrome P-450 is involved with the aromatic hydrocarbon-inducible N-hydroxylase activity, and that these genetic differences among inbred strains of mice offer a valuable experimental model system for studying the mechanism of hepatotoxicity and carcinogenicity among siblings of a defined genotype.

61. TRANSPLACENTAL INDUCTION OF CARCINOGEN-HYDROXYLATING SYSTEMS WITH 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN.

Berry DL, Zachariah PK, Namkung MJ, Juchau MR
Dept. Pharmacology, Sch. Medicine, Univ. Washington, Seattle, WA 98195
Toxicol Appl Pharmacol; 36(3):569-584 1976

The effects of a highly toxic herbicide contaminant 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) upon the hydroxylation rates of N-2-fluorenylacetamide (FAA) and benzo[a]pyrene (BP) were studied in fetal livers, placentas, maternal livers, and adrenal glands of pregnant Sprague-Dawley rats. Aryl hydrocarbon hydroxylase (AHH) activity was increased 14- and 100-fold in maternal and fetal livers, respectively, but there were only minimal increases in placentas and adrenal glands. Similar results were obtained with respect to the 7-, 3-, N-, 3-, and 1-hydroxylation rates of FAA. There was extensive cellular damage in the placentas as well as pathologic changes in fetal and maternal livers. Electron microscopy showed enlarged mitochondria and extensive glycogen deposition in maternal and fetal livers and increases in the amounts of rough endoplasmic reticulum in fetal livers. High-pressure liquid chromatography showed that the formation of diols (relative to phenols) was markedly increased in fetal and maternal livers following treatments with TCDD. The results suggested that the relative lack of response of fetal hepatic mixed-function oxidase systems to commonly employed inducing agents (polycyclic aromatic hydrocarbons) was not due to a lack of appropriate structural and/or regulatory genes required for the expression of enzyme induction during fetal life. (42 refs)

62. TRANSPLACENTAL STIMULATION OF BENZO(A)PYRENE (BP) METABOLISM IN EXTRAHEPATIC TISSUES BY 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN(TCDD) (MEETING ABSTRACT).

Berry DL, Zachariah PK, Slaga TJ, Juchau MR
Depts of Pharmacology and Anesthesiology Univ of Washington, and Fred Hutchinson Cancer Research Center, Seattle, Wa 98195.
Fed Proc; 35(3):409 1976

The effects of the highly toxic herbicide contaminant TCDD (2.5 microg/kg, ip) were studied in fetal livers, lungs and skin, placentas and maternal livers, lungs and adrenal glands of Sprague-Dawley rats. Aryl hydrocarbon hydroxylase activities were increased 14- and 100-fold in maternal and fetal livers respectively, 8- and 25-fold in maternal and fetal lungs, 30-fold in fetal skin, but only minimally in placentas and adrenal glands. Analyses of BP metabolism with high pressure liquid chromatography showed that maternal livers produced large quantities of several metabolites that were more polar than the dihydrodiols. Ratios of diols/phenols were highest in: Fetal lungs > maternal livers > fetal livers > maternal lungs > fetal skin > placentas. Epoxide hydrase activity was investigated with BP-4,5-oxide as substrate. The specific activities were highest in: The maternal liver > fetal liver > maternal lung > fetal lung > fetal skin. The capacity of the various tissues to catalyze covalent binding of BP to DNA in vitro correlated well with theoretical expectations regarding the relative activites of the enzyme systems investigated. (Author Abstract)

63. TRANSPLACENTAL INDUCTION OF MIXED-FUNCTION OXYGENASES IN EXTRA-HEPATIC TISSUES BY 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN.

Berry DL, Slaga TJ, Wilson NM, Zachariah PK, Namkung MJ, Bracken WM, Juchau MR
Dept. Pharmacology, Sch. Medicine, Univ. Washington, Seattle, WA 98195
Biochem Pharmacol; 26(15):1383-1388 1977

A study was made of the induction of aryl hydrocarbon hydroxylase (AHH) activity in the hepatic and extrahepatic tissues of both fetuses and mother rats following exposure of pregnant Sprague-Dawley rats to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). Further study was made of the ability of the various tissues to metabolize benzo(a)pyrene (BP). On day 20, following a single ip dose of 6.0 ug/kg TCDD on day 17 of gestation, AHH was induced 24-, 22-, 60-, and 4-fold in fetal lung, kidney, liver, and skin, respectively; maternal lung, kidney, liver and adrenal AHH was increased 4-, 2-, 30-, and 2-fold, respectively. High-pressure liquid chromatographic analysis of BP metabolism after TCDD induction indicated that fetal lung, kidney, and skin produced significant quantities of BP-7,8-diol, BP-4,5-diol,

and the 9-and 3-phenols of BP. Maternal lung also produced BP-9,10-diol, but maternal adrenal gland yielded primarily the 9-phenol of BP. Epoxide hydratase activity was increased two- to threefold in maternal lung, fetal lung, and skin after TCDD pretreatment, but was not affected significantly in liver, kidney, or placenta. It is concluded that TCDD provides a potent and broad-spectrum transplacental induction of carcinogen-transforming enzymes in extrahepatic tissues. (41 Refs)

64. METABOLIC ACTIVATION/DEACTIVATION REACTIONS DURING PERINATAL DEVELOPMENT.

Lucier GW, Lui EM, Lamartiniere CA
Natl. Inst. Environmental Health Sciences, Research Triangle Park, NC, 27709

Environ Health Perspect; 29:7-16 1979

The role of metabolic activation/deactivation reactions during development is evaluated in relation to developmental pharmacology and toxicology. Enzyme systems evaluated include the mixed-function oxidases (aryl hydrocarbon hydroxylase and oxidative demethylation), epoxide hydration and conjugation (glutathione conjugation, sulfation, and glucuronidation). Placental transfer and milk secretion of chemicals are discussed in relation to maternal, placental, and fetal metabolism. Normal patterns of enzyme development can be modified in two ways: (1) enzyme induction and (2) enzyme imprinting. Postnatal induction of the mixed-function oxidases and glucuronyl-transferase following treatment of pregnant rats with TCDD is shown to be caused primarily by newborn exposure to TCDD in milk. Structure-activity relationships are defined for the perinatal induction of hepatic enzymes by the pure PCBs. PCBs are divided into two classes: P-450 inducers and P-448 inducers. Imprinting or programming of hepatic metabolism is a function of the sexual differentiation of enzyme activity; male and female activities are similar in prepubertal animals, whereas pronounced sex differences are evident in adults. Treatment of newborn rats (days 2-6) with diethylstilbestrol or testosterone resulted in a feminization (decrease) of mixed-function oxidation and glucuronidation in adult males. No changes were seen in immature males or females or adult females. This effect appears to be irreversible and is under pituitary-hypothalamic-gonadal control. In addition to the feminization of enzyme activity, neonatal exposure to hormonally active chemicals also feminizes the hepatic response to cadmium in resultant adult animals. (71 Refs)

65. GENETIC EXPRESSION OF ARYL HYDROCARBON HYDROXYLASE ACTIVITY. INDUCTION OF MONOOXYGENASE ACTIVITIES AND CYTOCHROME P1-450 FORMATION BY 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN IN MICE GENETICALLY 'NONRESPONSIVE' TO OTHER AROMATIC HYDROCARBONS.

Poland AP, Glover E, Robinson JR, Nebert DW
U. Rochester Sch. Med. Dent., N. Y.

J Biol Chem; 249(17):5599-5606 1974

The ip administration of aromatic hydrocarbons such as 3-methylcholanthrene, beta-naphthoflavone, or naphthacene induces several monooxygenase activities and the new formation of a spectrally distinct CO-binding cytochrome in genetically 'responsive' inbred mouse strains, but fails to induce these changes in genetically 'nonresponsive' inbred strains even at chronically high doses. Administration of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD, 40 microg/kg), however, causes induction of a similar magnitude in either 'responsive' or 'nonresponsive' mice of several monooxygenase activities and the new formation of cytochrome P1-450 in liver, bowel, lung, kidney, and skin. Application of TCDD (4 microg) to the skin of either 'responsive' or 'nonresponsive' mice induces aryl hydrocarbon hydroxylase activity more than sixfold in the skin and in the liver. These data demonstrate that genetically 'nonresponsive' mice have the structural and regulatory genes necessary for expression of the inducible microsomal monooxygenase activities and associated new formation of cytochrome P1-450 and that the defect in these mice is a failure to recognize aromatic hydrocarbons which are less potent inducers.

66. THE GENETIC EXPRESSION OF ARYL HYDROCARBON HYDROXYLASE ACTIVITY: EVIDENCE FOR A RECEPTOR MUTATION IN NONRESPONSIVE MICE.

Poland A, Kende A
Dept. Pharmacology and Toxicology, Univ., Rochester Sch. Medicine and Denistry, Univ. Rochester, Rochester, NY, 14642

Mechanisms of Carcinogenesis, Proceedings of the Cold Spring Harbor Conferences on Cell Proliferation. Vol. 4 (Book B), Hiatt HH, Watson JD, Winsten JA, ed. Cold Spring Harbor, Cold Spring Harbor Laboratory, Origins Of Human Cancer., 699 pp., 1977.

The nature of the aryl hydrocarbon (Ah) locus in the mouse was determined. Previous studies have shown that the Ah locus determines the expression of aryl hydrocarbon hydroxylase (AHH) activity and cytochrome P1-450; they also implicate the Ah locus in mediating the mutagenesis and carcinogenesis produced by certain polycyclic aromatic hydrocarbons (PAH). 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) was used to determine the nature of the Ah locus and how PAH stimulate AHH activity. TCDD was a potent inducer of hepatic AHH activity and cytochrome P1-450 in rats and in nonresponsive mice, which were not responsive to the inductive activity of 3-methylcholanthrene. Experimental evidence indicates that the hepatic cytosol from C57BL/6J mice contains a binding species with a high affinity for TCDD, that the binding properties of this cytosol species correspond extremely well to the properties predicted for the induction receptor, and that the mutation in nonresponsive strains of mice appears to result in a receptor with a diminished affinity for inducing ligands. It is postulated that the Ah locus codes for the cytosol binding protein, which serves as a cellular recognition site for PAH, TCDD, and similar compounds, and that the binding of these inducers to the receptor in some manner serves as a master switch to initiate the expression of numerous noncontiguous structural genes. (43 Refs)

67. GENETIC EXPRESSION OF ARYL HYDROCARBON HYDROXYLASE BY 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN: EVIDENCE FOR A RECEPTOR MUTATION IN GENETICALLY NON-RESPONSIVE MICE.

Poland A, Glover E
Univ. Rochester Sch. Medicine and Dentistry, Rochester, N.Y. 14642

Mol Pharmacol; 11(4):389-398 1975

The induction of hepatic aryl hydrocarbon hydroxylase activity by 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) was investigated in 14 inbred mouse strains. Female (4- to 9-wk-old) mice were given ip injections of p-dioxane (0.4 ml/kg) or various doses of TCDD in the same volume of solvent. 3-Methylcholanthrene (80 mg/kg) was administered ip in corn oil (8 ml/kg). Aryl hydrocarbon hydroxylase activity was assayed in 10,000 x g liver supernatants. All strains tested exhibited enzyme activity in response to TCDD. Enzyme activity of genetically 'nonresponsive' strains of mice that fail to respond to 3-methylcholanthrene was in-

duced by TCDD; however, the dose required was greater than for the genetically 'responsive' strains. The dose of TCDD that elicited half the maximal enzyme activity (ED50) in responsive strains, C57BL/6J, BALB/cJ, and A/J, was about 1 nM/kg; in the nonresponsive strains, DBA/2J, AKR/J, and SJL/J, the ED50 was at least 10 nM/kg. In the above strains, TCDD at 3 nM/kg failed to induce hepatic aryl hydrocarbon hydroxylase activity in nonresponsive mice, but elicited 70% or more of the observed maximal enzyme activity in responsive strains. In the 14 strains the phenotypic characteristic of aromatic hydrocarbon responsiveness or nonresponsiveness could be detected equally well by a challenge with 3-methylcholanthrene (0.3 mM/kg) or TCDD at 3 nM/kg. In all nonresponsive strains, a 10-fold higher dose of TCDD induced hepatic enzyme activity. The heterozygous offspring of C57BL/6J and DBA/2J parents were distinguishable from both parental strains by an intermediate sensitivity to TCDD. It is concluded that the genetically nonresponsive mice have the structural and regulatory genes necessary for the expression of aryl hydrocarbon hydroxylase. The most likely explanation of the defect in nonresponsive mice appears to be a mutation that results in an induction receptor site with a diminished affinity for inducing drugs leading to an almost absolute unresponsiveness to 3-methylcholanthrene and a diminished sensitivity to the more potent inducer, TCDD.

68. GENETIC DIFFERENCES IN INDUCTION OF CYTOSOL REDUCED-NAD(P):MENADIONE OXIDOREDUCTASE AND MICROSOMAL ARYL HYDROCARBON HYDROXYLASE IN THE MOUSE.

Kumaki K, Jensen NM, Shire JG, Nebert DW
Developmental Pharmacology Branch, Natl. Inst. Child Health and Human Development, NIH, Bethesda, MD 20014
J Biol Chem; 252(1):157-165 1977

The stimulation of NADPH:menadione oxidoreductase activity in liver cytosol was highly correlated with the stimulation of hepatic microsomal benzo(a)pyrene aryl hydrocarbon hydroxylase (AHH) activity in 3-methylcholanthrene (3-MC)-, beta-naphthoflavone-, phenobarbital-, or pregnenolone-16alpha-carbonitrile-treated inbred C57BL/6N and DBA/2N mice and in eight other inbred strains treated with 3-MC. No oxidoreductase activity was detectable in mouse liver microsomes. Cytochrome and 2,6-dichorophenolindophenol were equally good electron acceptors for the oxidoreductase. There was no preferential in vitro inhibition of induced vs control oxidoreductase activities by alpha-naphthoflavone or metyrapone. In 3-MC-treated F1 and F2 progeny and offspring from backcrosses between the F1 and either C57BL/6N or DBA/2N parent, there was no strict correlation between induced or noninducible AHH and oxidoreductase activities. 2,3,7,8-Tetrachlorodibenzo-p-dioxin, at doses of 80 ug/kg, induced the oxidoreductase about threefold in C57BL/6N and less than 50% in DBA/2N mice. The data are consistent with the hypothesis that two loci (Ox-1 and Ox-2) regulate oxidoreductase induction by 3-MC, that one of the genes is linked to the Ah locus (with an estimated recombination frequency between 2% and 23% , and that the other gene is not linked to the Ah locus. These experimental data might be useful in the protein activator hypothesis of the Britten-Davidson model for gene regulation. (50 Refs)

D.

Other Metabolic Effects Induced by Dioxins and Dibenzofurans by Experimental Animals

69. THE INFLUENCE OF PHENOBARBITAL, 3-METHYLCHOLANTHRENE, AND 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN ON GLUTATHIONE S-TRANSFERASE ACTIVITY OF RAT LIVER CYTOSOL.

Baars AJ, Jansen M, Breimer DD
Dept. Pharmacology, Univ. Leiden, Subfaculty Pharmacy, Sylvius Labs., Wassenaarseweg 72, Leiden, Netherlands
Biochem Pharmacol; 27(21):2487-2494 1978

The influence of the drug-metabolizing enzyme inducers, phenobarbital (PB), 3-methylcholanthrene (MC), and 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) on glutathione (GSH) S-transferase activity in rat liver cytosol was studied using styrene oxide (STOX), 1,2-butylene oxide (BOX), and 1-chloro-2,4-dinitrobenzene (CDNB) as the electrophilic substrates. Assuming Michaelis-Menten kinetics, apparent Km and Vmax values of the GSH S-transferase activities were calculated using a computer program. Pretreatment of the rats with MC (20 mg/kg ip 1x/day for 4 days) resulted in enhancement of all measured activities expressed in terms of cytosol protein, while TCDD administration (10 ug/kg ip 1x/day on days 1 and 7) enhanced only the activities expressed on a per gram body wt basis. PB administration (80 mg/kg ip 1x/day for 14 days) enhanced activities by both standards when STOX was the substrate, but when CDNB was the substrate, only the activity per gram body wt increased. All pretreatments increased the Vmax values when CDNB was the substrate, while PB and MC had enhancing effects when STOX was the substrate. The Vmax with BOX as substrate was enhanced only after TCDD administration. The Km values when BOX was the substrate were lowered after MC pretreatment. TCDD pretreatment decreased the Km for the STOX substrate, while it increased the Km for the CDNB substrate. It is concluded that the GSH S-transferase system is inducible. Qualitative differences were not observed between the inducing effects of PB and MC; however, TCDD administration resulted in a different induction pattern, which may indicate that during induction with this latter agent different types of GSH S-transferase are involved. (42 Refs)

70. GENETIC REGULATION OF UDP-GLUCURONOSYLTRANSFERASE INDUCTION BY POLYCYCLIC AROMATIC COMPOUNDS IN MICE. COSEGREGATION WITH ARYL HYDROCARBON [BENZO(A)PYRENE] HYDROXYLASE INDUCTION.

Owens IS
Developmental Pharmacology Branch, Natl. Inst. Child Health and Human Development, NIH, Bethesda, MD 20014
J Biol Chem; 252(9):2827-2833 1977

3-Methylcholanthrene (3-MC) induction of hepatic uridine diphosphate (UDP)-glucuronosyl-transferase was examined in various strains of mice to determine whether this activity is under genetic control. 3-MC induces the enzyme in C57BL/6N, A/J, PL/J, C3HeB/FeJ, and BALB/cJ mice, but not in DBA/2N, AU/SaJ, AKR/J, or RF/J inbred mice. Induction is max in C57BL/6N mice with 200 mg/kg 3-MC ip, but no induction occurs in DBA/2N mice with a dose of 400 mg/kg. The rise in activity lags 1 or more days behind inducible hydroxylase activity and peaks 5 days after 3-MC. In offspring from appropriate backcrosses and intercrosses between C57BL/6N and DBA/2N strains, the inducible trait is inherited as a codominant one. This expression differs from that of inducible hydroxylase activity, which is inherited almost exclusively as a single autosomal dominant trait. 2,3,7,8-Tetrachloro-dibenzo-p-dioxin (TCDD: 50 ug/kg ip) induced the transferase more than threefold in C57BL/6N mice and less than twofold in DBA/3N mice; hydroxylase was induced about eightfold in

both strains. When two 40-mg/kg doses of 3-MC were administered 3 days after 25 ug/kg TCDD, there was no enhancement of the rise in inducible transferase activity seen in mice that received TCDD alone. These results indicate that the inducibility of transferase and hydroxylase activities may be regulated by the same genetic locus (Ah) most likely through a common cytosolic receptor, and that although hydroxylase can be induced in DBA/2N mice by TCDD prior to MC treatment, MC metabolites are incapable of inducing further transferase activity. (39 Refs)

71. INDUCTION OF DT-DIAPHORASE BY 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN.

Beatty P, Neal RA
Vanderbilt Univ Sch Medicine, Nashville, TN 37232
Biochem Biophys Res Commun; 68(1):197-204 1976

The ability of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) to induce hepatic DT-diaphorase activity in male Sprague-Dawley rats was examined. Diaphorase activity was assayed by following the reduction of 2,6-dichlorophenol indophenol at 600 nm. A single ip injection of 90 u/kg of TCDD resulted in a rapid rise in diaphorase activity in both cytosol and microsomes to a level approximately six-fold above olive oil-treated controls after 24 hr. Maximal induction of microsomal NADPH diaphorase was achieved in 24-48 hr, while approximately seven days were required for maximal induction in the cytosol. This maximal level in both cytosol and microsomes was maintained for at least 15 days postinjection. At lower doses of TCDD the onset of induction was less rapid. Howeve:, maximal induction was obtained at about seven days with all doses examined (5.63, 11.25, 22.5, and 45 ug/kg). There was a roughly linear relationship between NADH diaphorase and NADPH diaphorase activity at seven days and the dose of TCDD administered (linear regression correlation coefficient of 0.895 and 0.725, respectively). The authors conclude that TCDD is approximately 17,000 times more potent as an inducer of diaphorase activity than 3-methylcholanthrene.

72. DIFFERENT EFFECT OF 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN ON GLUCURONIDE CONJUGATION OF VARIOUS AGLYCONES. STUDIES IN WISTAR AND GUNN RATS.

Aitio A, Parkki MG, Marniemi J
Dept. Physiology, Univ. Turku, Kiinamyllynkatu 10, SF-20520 Turku 52, Finland
Toxicol Appl Pharmacol; 47(1):55-60 1979

The effect of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD: 20 ug/kg intragastrically) on the activity of uridine diphosphate-glucuronosyltransferase (UDPGT) in the liver and kidney was studied in adult Gunn (G), Wistar (W), and W-G hybrid rats. In the W rats, TCDD caused an 8-fold increase in liver UDPGT activity toward 4-methylumbelliferone (4-MU), a 2-fold increase in kidney UDPGT toward 4-MU, an 8-fold increase in the liver conjugation of o-aminophenol (o-AP), and p-nitrophenol (p-NP), a 2-fold increase in the renal conjugation of o-AP and p-NP, and no effect on the hepatic or renal conjugation of bilirubin. In the W-G hybrids, TCDD caused a 5-fold increase in the liver conjugation of 4-MU, a 2-fold increase in the kidney conjugation of 4-MU, a 7-fold increase in the liver conjugation of o-AP and p-NP, and a 2-fold increase in the kidney conjugation of o-AP and p-NP; there was no effect on the activity of UDPGT toward bilirubin. TCDD had no effect on the hepatic or renal conjugation of any aglycone in the Gunn rats. Diethylnitrosamine (15 mM in the in vitro incubation mixture) had no effect on the conjugation of 4-MU, nonsignificantly decreased the conjugation of bilirubin, markedly increased the hepatic activity of UDPGT in untreated (especially G) rats, and had no effect on the hepatic or renal conjugation of o-AP or p-NP in the TCDD-treated rats. (24 Refs)

73. COMPARISON OF PHENOBARBITAL- AND CARCINOGEN-INDUCED ALDEHYDE DEHYDROGENASES IN THE RAT.

Marselos M, Torronen R, Koivula T, Koivusalo M
Dept. Physiology, Univ. Kuopio, Kuopio 10, Finland
Biochim Biophys Acta; 583(1):110-118 1979

The induction of liver aldehyde dehydrogenase (AD) activity by 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD, 80 ug/kg, ip), phenobarbital (PB, 1 mg/ml in the drinking water for 7 days), 2-acetamidofluorene (AAF, 0.02% of the diet for 3 mo), and various carcinogenic agents was studied in Sprague-Dawley (chronic AAF treatment only) and Wistar/Af/Han/Mol/(Han 67) rats. Substrain rr of the latter strain showed no induction of liver or intestinal postmitochondrial fraction AD activity after PB, whereas both activities were increased (7-and 2-fold, respectively) in substrain RR rats. TCDD caused a 40-fold increase in liver AD and a significant increase in serum AD in both strains. Acute administration of AAF or urethan (100 mg/kg intragastrically for 4 days) had no effect on the liver or small intestinal AD of rr rats, whereas a 40-fold increase was seen after 3-methylcholanthrene (100 mg/kd), a 30-fold increase after benzo(a)pyrene (100 mg/kg), and a 2-fold increase after chrysene (200 mg/kg). The latter three compounds were also given intragastrically for 4 days. Chronic AAF administration resulted in a 15-fold increase in liver AD. The activities induced by TCDD and the carcinogens showed similar isoelectric focusing patterns in gel slabs and similar mol wts, as determined by gel chromatography. These activities were clearly differentiated from the normal cytoplasmic activity and from that induced by PB. (19 Refs)

74. DISPOSITION OF TETRACHLORODIBENZOFURAN IN MALE RATS (MEETING ABSTRACT).

Birnbaum LS, Decad GM, Matthews HB
NIEHS, Research Triangle Park, NC, 27709
Fed Proc; 39(3,part2):999 1980

2,3,7,8-Tetrachlorodibenzofuran (TCDF) is an extremely toxic environmental pollutant found as a contaminant in commercial polychlorinated biphenyls and pentachlorophenol mixtures. The distribution of 14C-TCDF (purity greater than 99%) was studied in 200-250 mg male Fischer 344 rats after po and iv administration. TCDF was completely absorbed at two dose levels (0.1 and 1.0 umoles/kg). The liver was the main site of TCDF accumulation, with lesser amounts being present in the adipose tissues and skin. However, within 3 days, less than 5% of the initial dose remained in the liver or fat and less than 2% remained in the skin, with no other tissues exhibiting significant amounts of radioactivity. More than 50% of the administered dose was excreted in the feces within 48 hr and greater than 90% within 5 days. Approx 3% of the dose was eliminated in the urine within 5 days. In studies of biliary excretion, 5% of the radioactivity initially administered as TCDF was excreted in the bile within 4 hr as one or more metabolites of TCDF. None of the meterial removed co-chromatographed with the parent compound. Thus, TCDF is completely absorbed, concentrated in the liver, fat and skin, metabolized, and excreted primarily by the fecal route. (no Refs)

75. DISPOSITION AND EXCRETION OF 2,3,7,8-TETRACHLORODIBENZOFURAN IN THE RAT.
Birnbaum LS, Decad GM, Mathews HB
Environmental Biology Branch, National Institute of Environmental Health Sciences, Research Triangle Park, N.C. 27709
Toxicol Appl Pharmacol; 55:342-352 1980

III. METABOLIC EFFECTS OF DIOXINS AND DIBENZOFURANS IN IN VITRO SYSTEMS

76. INDUCTION, INHIBITION, AND BIOLOGICAL PROPERTIES OF ARYL HYDROCARBON HYDROXYLASE IN A STABLE HUMAN B-LYMPHOCYTE CELL LINE, RPMI-1788.
Freedman HJ, Parker NB, Marinello AJ, Gurtoo HL, Minowada J
Dept. Experimental Therapeutics, Roswell Park Memorial Inst., New York, NY, 14263
Cancer Res; 39(11):4612-4619 1979

The induction and inhibition of aryl hydrocarbon hydroxylase (AHH) by various chemicals in a stable, human B-lymphocyte cell line (RPMI-1788) are reported, together with the kinetic and biological properties of the enzyme in these cells. Over the dose ranges tested and on molar basis the inducers, in decreasing order of potency, were 2,3,7,8-tetrachlorodibenzo-p-dioxin, dibenz(a,h)-anthracene, 3-methylcholanthrene, benzo(a)pyrene, and 1,2-benzanthracene. Potential inducers that, paradoxically, diminished basal AHH included 7,12-dimethylbenzanthracene, 2,5-diphenyloxazole, and chrysene. Induction under optimal culture conditions ensured maximal activities three- to four-fold above basal AHH. The characteristics of the induced [dibenz(a,h)anthracene] and basal enzymes were indentical. Both had similar pH curves (optima at 8.25) and inhibitor specificity (alpha- and beta-naphthoflavones, metyrapone, and 2-diethylaminoethyl-2,2-diphenylvalerate in decreasing potency). Induced and basal enzymes exhibited similar half-lives (41 and 46 hr), apparent activation energies (16.7 and 16.6 kcal/mol), temperature optima (37-38 C and 38-39 C), temperature-dependence of denaturation (range, 42-50 C), and apparent Km with benzo(a)pyrene (1.8 and 0.8 uM). The small difference in the apparent Km was related to enzyme concentration in the incubation medium rather than to the quality of the enzyme. (56 Refs)

77. EFFECTS OF MICROSOMAL STIMULATORS ON THE IN VITRO METABOLISM OF 2,5,2',5'-TETRACHLOROBIPHENYL (TCB), A COMPONENT OF CARCINOGENIC POLYCHLORINATED BIPHENYL MIXTURES (MEETING ABSTRACT).
Preston BD, Seymour JL, Kordes J, Hsia MT, Allen JR
Univ. Wisconsin, Madison, WI, 53706
Proc Am Assoc Cancer Res; 19:200 1978

This study was designed to determine the quantitative effects of specific microsomal enzyme stimulators on the in vitro production of chemically active metabolites of 2,5,2',5'-tetrachlorobiphenyl (TCB) and to identify the metabolites thus produced. Microsomes isolated from male rats pretreated with 3-methylcholanthrene (3MC), 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), or 3,4,3',4'-tetrachloroazobenzene (TCAB) and from untreated control rats were incubated with tritiated TCB in the presence of an NADPH-generating system. Fractionatioc into 5% trichloroacetic acid (TCA)-soluble tritium followed by exhaustive methanol extraction to yield macromolecular pellet-bound tritium showed marked differences among the various treatments. When compared to controls, TCA-soluble tritium and the pellet-bound tritium were increased 14 x and 8 x, respectively, after phenobarbitol stimulation with a concomitant significant decrease in the apparent Km values of these two fractions. Pretreatment with 3MC or TCDD depressed the amount of tritium in both fractions, while TCAB stimulation acted only to decrease the pellet-bound portion. Chromatographic and mass spectral analysis demonstrated the production of monohydroxy-, dihydroxy-, and dihydrodiol-TCB metabolites in the phenobarbitol-stimulated system. It is concluded that aryl hydrocarbon hydroxylases stimulated by 3MC, TCDD, and TCAB are not responsible for active metabolism of TCB in vitro, whereas phenobarbitol-stimulated enzymes enhance TCB metabolism probably via an epoxide intermediate.

78. CYTOSOLIC RECEPTOR FOR ARYL HYDROCARBON HYDROXYLASE INDUCTION BY POLYCYCLIC AROMATIC COMPOUNDS. EVIDENCE FOR STRUCTURAL AND REGULATORY VARIANTS AMONG ESTABLISHED CELL CULTURE LINES.
Guenthner TM, Nebert DW
Developmental Pharmacology Branch, National Inst. Child Health and Human Development, NIH, Bethesda, MD 20014
J Biol Chem; 252(24):8981-8989 1977

The effective doses of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) for inducing half-maximally (ED50 values) aryl hydrocarbon (benzo[a]pyrene) hydroxylase activity (EC 1.14.14.2) in H-4-II-E, Hepa-1, VERO, and HTC established cell culture lines are about 0.23, 0.45, 10, and greater than 200 nanoM, respectively, and the max induced hydroxylase activity is more than 100 x higher in TCDD-treated H-4-II-E and Hepa-1 than in VERO or HTC lines. The former two lines are therefore regarded as 'responsive,' and the latter two 'nonresponsive,' to TCDD. The apparent Kd values for TCDD binding to a small, saturable, homogeneous population of cytosolic sites in all four of these cell lines are similar, however, ranging between 1.02 and 2.80 nanoM. The estimated mean numbers of cytosolic binding sites are also similar, ranging between 1400-2200/cell in all four of these cell lines grown in control growth medium. The curve for high affinity TCDD binding is sigmoidal in shape, perhaps reflecting positive cooperativity. 3-Methylcholanthrene (MC), benzo[a]anthracene (BA), and beta-naphthoflavone - three known inducers of aryl hydrocarbon hydroxylase activity - are capable of displacing 3H-TCDD from the receptor similarly in all four cell lines, but the avidity of the receptor for TCDD is about 100 to greater than 1000 x greater than that for these three other inducers. Phenobarbital, pregnenolone-16-alpha-carbonitrile, dexamethasone, and two inactive congeners of TCDD are incapable of displacing H3-TCDD from the receptor at concentrations 10 greater than that of H3-TCDD. The receptors in the two responsive cell lines differ from those in the two nonresponsive cell lines with regard to relative thermolability in the absence of TCDD: the former are significantly more protected from denaturation at 45 C for 10 min in the presence of TCDD but the latter are not. During induction of the hydroxylase in the responsive cell lines by MC or BA there are increases ranging between 60-140% in high affinity TCDD binding sites 24 and 48 hr after polycyclic hydrocarbon treatment. The increase in receptors is greater in cells during logarithmic growth than during the stationary phase. This increase does not occur in the MC- or BA-treated nonresponsive cell lines. These data indicate that the presence

of cytosolic high affinity binding sites is not necessarily associated with aryl hydrocarbon hydroxylase inducibility regulated by the Ah locus. However, the increase in these cytosolic binding sites appears to be directly associated with the pleiotypic response governed by the Ah locus, one of the responses being induction of the hydroxylase activity. (Author abstract) (65 Refs)

79. INDUCTION OF 2-ACETYLAMINOFLUORENE (AAF) N- AND C-HYDROXYLATION IN ISOLATED RAT HEPATOCYTES (MEETING ABSTRACT).

Smith CL, Thorgeirsson SS
LCHPH, NCI, NIH, Bethesda, MD, 20205
Pharmacologist; 21(3):212 1979

The reduction of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) and polycyclic aromatic hydrocarbon inducible monooxygenase activities in livers from rabbits, mice and rats is under temporal control, ie different forms of cytochrome P-450 are induced in the neonate and the adult animals. Since neoplastic tissues acquire many fetal characteristics, we examined the TCDD induction of 2-acetylaminofluorene (AAF) N- and C-hydroxylation in isolated normal and neoplastic hepatocytes. The hyperplastic liver nodules and hepatomas were produced according to Solt et al and the hepatocytes were isolated by the method of Seglen. TCDD induced both C- and N- hydroxylation of AAF in adult normal hepatocytes whereas only the induction of C-hydroxylation (principally 7-and 5-hydroxylation) is maintained in hepatocytes from early hyperplastic nodules. The induction in hepatocytes from hepatomas was restricted to C-hydroxylation and the degree of induction differed according to differentiation stage of the hepatomas. It is concluded that the regulation of monooxygenase induction to TCDD in neoplastic rat liver tissue is under similar control as observed in fetal and neonatal liver. (4 Refs)

80. ARYL HYDROCARBON HYDROXYLASE ACTIVITY OF TWENTY-THREE HALOGENATED DIBENZO-P-DIOXINS (MEETING ABSTRACT).

Bradlaw JA, Garthoff LH, Hurley NE, Firestone D
Food and Drug Admin., Washington, DC
Toxicol Appl Pharmacol; 37(1):119 1976

Twenty-three halogenated isomers of dibenzo-p-dioxin of known chemical purity, dibenzo-p-dioxin and a predioxin, 4,5,6-trichloro-2-(2,4-dichlorophenoxy) phenol were tested for induction of aryl hydrocarbon (benzo[a]pyrene, BAP) hydroxylase activity in rat hepatoma cell cultures. Plates containing 24 hr cultures were challenged for 72 hr with picomole (pmol) quantities of test compound dissolved in dimethyl sulfoxide. The plates, with about 3 x 10 cells, were scraped, and aryl hydrocarbon hydroxylase (AHH) activity was determined in homogenized cell extracts by conversion of BAP to 3-OH BAP. Specific enzyme activity was expressed as pmol of product formed/milligram of protein/min at 37 C. Limits of detection and experimental variability were determined, and dose-response curves of AHH activity were plotted. The dose that produced 50% of the max enzyme activity was determined for the reactive compounds using 2,3,7,8-tetrachlorodibenzo-p-dioxin as the standard compound in each experiment. The estimated doses (pmol) for the reactive dibenzo-p-dioxins were as follows: 2,3,7,8-tetrachloro-(1.08); 2,3,7,8-tetrabromo-(3.64); 1,2,3,7,8-pentachloro-(20.5); 1,2,3,4,7,8-hexachloro-(49.9); 1,2,3,7,8,9-hexachloro-(84.5); 1,3,7,8-tetrachloro-(114); 1,2,3,4,7-pentachloro-(121); 1,2,3,4,6,7,8-heptachloro-(129); 1,2,3,6,7,8-hexachloro-(701); 1,2,3,8-tetrachloro-(3300); octachloro-(3400); 1,2,3,4,6,7,9-heptachloro-(3790); and 2,3,7-trichloro-(4600). Detectable but nonquantifiable responses at the 5,000-pmol dose level were obtained with 2,7-dichloro-; 1,2,4,7,8-pentachloro-; and 1,2,3,6,7,9-hexachloro-isomers. No detectable responses were obtained at the highest level tested (5,000 pmol) with dibenzo-p-dioxin; 1,3-dichloro-; 1,6-dichloro-; 2,3-dichloro-; 2,8-dichloro-; 1,2,3,4-tetrachloro-; 1,3,6,8-tetrachloro-; and 1,2,4,6,7,9-hexachloro-isomers. The predioxin exhibited no detectable response at 50,000 pmol. This induction of AHH activity demonstrates a sensitivity to dibenzo-p-dioxins, which have halogen atoms in at least three of the four lateral ring positions. (no refs)

81. RAT LIVER ALDEHYDE DEHYDROGENASE - IMMUNOCHEMICAL IDENTITY OF 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN INDUCIBLE NORMAL LIVER AND 2-ACETYLAMINOFLUORENE INDUCIBLE HEPATOMA ISOZYMES.

Lindahl R, Roper M, Deitrich RA
Developmental Biology Section, Dept. Biology, Univ. Alabama, University, AL, 35486
Biochem Pharmacol; 27(20):2463-2465 1978

Aldehyde dehydrogenase (ALDH) isozymes in 2-acetylaminofluorene-induced rat hepatomas were studied immunochemically. In Ouchterlony immunodiffusion assays, rabbit antisera against 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD)-induced normal liver ALDH alpha and tau isozymes formed precipitin lines with hepatoma-specific alpha isozymes. Hepatoma-specific antibody against hepatoma-specific alpha isozyme reacted with complete identity with normal liver TCDD-induced tau isozyme. Neither anti-alpha nor anti-tau serum reacted with phenobarbital-induced rat liver ALDH phi isozyme. Thus, the alpha and tau isozymes are not related immunochemically to the phi isozyme. (21 Refs)

82. INDUCTION OF UDP-GLUCURONOSYLTRANSFERASE ACTIVITY IN THE REUBER H-4-II-E HEPATOMA CELL CULTURE.

Malik N, Koteen GM, Owens IS
Developmental Pharmacology Branch, NICHHD, NIH, Bethesda, MD, 20205
Mol Pharmacol; 16(3):950-960 1979

Inducer compounds were examined. Reuber cells in logarithmic growth were treated with the appropriate inducer and transferase activity was assayed by fluorescence of 4-methylumbelliferone, the acceptor substrate. Isoproterenol, phenobarbital (PB), benzo(a)pyrene (BP) and benz(a)anthracene (BA) caused an approx 4-fold increase in specific transferase activity which peaked at 48 hr. Activity after exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) and 3-methylcholanthrene (MC) peaked at 72 hr. TCDD caused a 6-fold increase. BP was an inducer superior to seven BP phenols, to BP-9,10-diol, and to BP-6,12-quinone. Other metabolites of BP, BA, and MC did not induce transferase activity. Any combination of PB and MC, BA, or TCDD caused more induction than the compounds alone; combinations of two aromatic compounds did not cause additive transferase activity. Three classes of inducers already known to exist for monooxygenase activity in cell cultures also induced transferase activity. The rise of TCDD-induced transferase activity was progressively inhibited by exposure to increasing concentrations of actinomycin D (AD) or cycloheximide (CH). A rapid rise in transferase activity occurred if cells were first exposed to TCDD and CH for 12 hr followed by AD. Initial synthesis of messenger RNA and continuous protein synthesis appeared to be needed for induction of transferase activity. (30 Refs)

83. STUDIES ON THE REQUIREMENTS FOR INDUCTION OF UDP GLUCURONOSYL-TRANSFERASE (T'ASE) ACTIVITY IN THE REUBER HEPATOMA H-4-II-E ESTABLISHED CELL LINE (MEETING ABSTRACT).

Malik N, Owens IS
NICHD, NIH, Bethesda, MD 20014
Pharmacologist; 19(2):150 1977

4-Methylumbelliferone T'ase activity in the cultured rat Reuber hepatoma cell line is induced 1.5-4 fold by a number of polycyclic aromatic compounds (PAC), including benzo[a]pyrene, benz[a]anthracene, 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), 3-methylcholanthrene and beta-naphthoflavone, by phenobarbital, and by the biogenic amine isoproterenol. The 6,12-quinone of benzo[a]pyrene induces T'ase activity while the 1,6-or 3,6-quinone, the 3-, 6-, 7-, or 9-phenol and the 4,5- or 7,8-dihydrodiol do not. Combinations of phenobarbital with a PAC caused additive effects on the induced level of T'ase activity. TCDD in the presence of actinomycin D or cycloheximide does not induce T'ase activity. However, actinomycin D added to cultures 24 hr after TCDD does not affect the further rise in T'ase activity. Cycloheximide added simultaneously with TCDD prevents induction, but the replacement of cycloheximide with actinomycin D causes an even faster rise in activity than the effect of TCDD alone. The general requirements of nonmetabolized PAC's, initial RNA synthesis, and continuous protein synthesis for T'ase induction are similar to the requirements (previously published) for the metabolically coordinated enzyme, aryl hydrocarbon, benzo[a]pyrene hydroxylase. (no Refs)

84. HEPATIC AND EXTRAHEPATIC METABOLISM OF C-STYRENE OXIDE.

Ryan AJ, James MO, Ben-Zvi Z, Law FC, Bend JR
Pharmacology Branch, Natl. Inst. Environmental Health Sciences, Research Triangle Park, NC 27709
Environ Health Perspect; 17:135-144 1976

The activities of the epoxide-metabolizing enzymes glutathione S-transferase (GT) and epoxide hydrase (EH), with 8-C-styrene oxide as substrate, were studied in subcellular fractions of liver, lungs, kidney, and intestinal mucosa of rabbits, guinea pigs, perinatal and adult rats, and rats pretreated with phenobarbital (PB), 1,2,3,4-dibenzanthracene, pregnenolone-16alpha-carbonitrile (PCN), and 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), and also in isolated perfused rat liver and rabbit lungs. The liver had the highest GT and EH activities in each species. The liver and kidney GT activities were higher in the rat and guinea pig than in the rabbit. Rat testis also had appreciable GT activity. In perinatal rats, EH and GT developed at different rates in each tissue. PB pretreatment increased both enzyme levels in the livers of rats of both sexes; PCN pretreatment induced only GT in the female liver. TCDD doubled renal EH activity and PB increased intestinal EH activity in both sexes, but the other extrahepatic EH and GT levels were unaffected by any pretreatment. When styrene oxide biotransformation was studied in isolated perfused rat liver and rabbit lung preparations, conjugation with glutathione was a major metabolic pathway, although significant amounts of diol were also formed. In rat liver, 27%-40% of the administered styrene oxide was excreted via the bile, mainly as S-(1-phenyl-2-hydroxyethyl)glutathione. (23 Refs)

85. EFFECTS OF PRETREATMENT WITH 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN ON THE CAPACITY OF HEPATIC AND EXTRAHEPATIC MOUSE TISSUES TO CONVERT PROCARCINOGENS TO MUTAGENS FOR SALMONELLA TYPHIMURIUM AUXOTROPHS.

DiGiovanni J, Berry DL, Slaga TJ, Jones AH, Juchau MR
Dept. Pharmacology, Sch. Medicine, Univ. Washington, Seattle, WA, 98195
Toxicol Appl Pharmacol; 50(2):229-239 1979

The capacity of hepatic and extrahepatic tissues from female CD-1 mice pretreated with 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD; 1 ug ip) to convert 7,12-dimethylbenz(a)anthracene (DMBA), benzo(a)pyrene (BP), and N-2-fluorenylacetamide (FAA) to metabolites mutagenic to Salmonella typhimurium strains TA-98 and TA-100 was greater than that observed in untreated control mice. Increases in monoxygenase activities in treated tissues roughly paralleled those in controls. FAA was generally converted to metabolites that produced more mutations than did metabolites of either BP or DMBA. For kidney tissues, TCDD pretreatment generated only very minor amounts of mutagens from FAA. For pulmonary tissues, TCDD pretreatment resulted in slight decreases in the formation of mutagenic intermediates from DMBA. TCDD pretreatment produced 2-to 10-fold increases in the quantity of most of the major metabolites produced by incubation of DMBA with hepatic, pulmonary, and renal S-9 fractions. Pronounced increases in quantities of metabolites were also observed following incubation of BP with pretreated hepatic, pulmonary, and renal fractions. Phenolic compounds were the major metabolites in each case. In the kidney, treatment with TCDD resulted in a 50% decrease in amounts of the N-hydroxylated FAA product and a decrease in the 1-hydroxy derivative. Quantities of the major FAA metabolite (7-hydroxy-FAA) were markedly increased by TCDD pretreatment. The results suggest an overall positive correlation between monooxygenase activities of various mouse tissue preparations and their capacity to convert procarcinogens to mutagens in the Salmonella mutagenesis assay. (20 Refs)

86. 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN: FAILURE TO DEMONSTRATE TOXICITY IN TWENTY-THREE CULTURED CELL TYPES.

Knutson JC, Poland A
McArdle Lab. Cancer Res., Univ. Wisconsin, Madison, WI, 53706
Toxicol Appl Pharmacol; 54(3):377-383 1980

Twenty-three cultured cell types were investigated for a toxic response to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD: 10(-7), 10(-9), and 10(-10) M). The cell types included rat hepatoma cells, mouse embryonal carcinoma cells, mouse embryonal fibroblasts, human foreskin fibroblasts, human urinary epithelium, primary adult rat hepatocytes, primary embryonic chick and mouse fibroblasts, mouse lymphoma cells, mouse leukemia cells, mouse erythroleukemia cells, mouse lymphocytes, and human WBC. A toxic response was defined as a pronounced alteration in the morphology of the cells or culture, the percentage of viable cells, or the growth rate in TCDD-treated cultures as compared with controls. Induction of aryl hydrocarbon hydroxylase (AHH) activity by TCDD was assayed to determine the presence of the receptor that appears to mediate the pleiotropic response to TCDD. No toxic effect of TCDD was demonstrated in any cell type, including those responding to TCDD with the induction of AHH activity. (31 Refs)

87. STUDIES ON THE INDUCTION OF SISTER CHROMATID EXCHANGE IN HUMAN FIBROBLASTS BY DIETHYLSTILBESTROL (MEETING ABSTRACT).

Haenisch FT, Rudiger HW
I. Medizinische Klinik, Univ. Hamburg, Hamburg, W. Germany
Clin Genet; 14(5):291-292 1978

We studied the induction of sister chromatid exchanges (SCE) in human diploid fibroblasts in the presence of diethylstilbestrol (DES). The cells in culture were inoculated with bromodeoxyuridine (30 ug/ml) and the compound was tested for 72 hr. After staining with acridine-orange, the SCE were directly evaluated under a fluorescent microscope. The initial experiment revealed that DES induces a flat increase of SCE, which leads to a plateau at concentrations over 300 nanomolar. We did the same experiment again with control cell lines of five different male and female donors, and got identical results. Since the induction of SCE was inhibited by naphthoflavone (ANF, 5 ug/ml) and enhanced by 1,2,7,8-tetra-chloro-dibenzo-p-dioxin (TCDD 10(-10) M), we supposed that reactive metabolities are possibly involved (as for instance diethylstilbestrol-epoxide and dienestrol), which could be generated by means of a mixed function oxidase (MFO). When diethylstilbestrol-epoxide is added to the culture medium instead of DES, there is a higher increase of SCE at lower concentrations as compared with DES. This is even more pronounced with dienestrol: though the highest amount of SCE is induced by diethylstilbestrol-epoxide, the concentration for half maximal induction of SCE is 8 x higher with diethylstilbestrol-epoxide than with dienestrol. The SCE rates induced by dienestrol were reduced to almost control levels by ANF; those induced by diethylstilbestrol-epoxide, however, were only slightly reduced. An induction of MFO by TCDD, on the other hand, resulted in a further increase of SCE with DES and with dienestrol, while TCDD and DES were producing less SCE than TCDD alone. Thus, DES is testable in a short-term carcinogenicity assay; it is possibly activated enzymatically by a MFO to dienestrol and to diethylstilbestrol-epoxide; and diethylstilbestrol-epoxide is possibly an ultimate carcinogen. (no Refs)

88. GENETIC EFFECTS OF CHLORINATED ANILINES AND AZOBENZENES ON SALMONELLA TYPHIMURIUM.

Gilbert P, Saint-Ruf G, Poncelet F, Mercier M
Lab. Biotoxicology, Univ. Louvain, UCL 7369, B-1200 Brussels, Belgium
Arch Environ Contam Toxicol; 9(5):533-541 1980

The genetic effects of several structurally related chlorinated anilines and azobenzenes on Salmonella typhimurium (ST) were studied. Negative results were obtained with 4-chloroaniline, 1-chloro,2-nitrobenzene, 1-chloro,4-nitrobenzene, 3,4-dichloroaniline, 3,4,3',4'-tetrachloroazobenzene (TCAB), 3,4,3',4'-tetrachloroazoxybenzene, 2,5,2',5'-tetrachloroazobenzene, 2,3,2',2'-tetrachloroazobenzene, 2,4,2',4'-tetrabromoazobenzene, 2,4,2',4'-tetrachloroazobenzene, 2,3,4,2',3',4'-hexachloroazobenezene, 2,4,5,2',5'-hexachloroazobenzene, 3,4,5,3',4',5'-hexachloroazobenzene, and 2,3,7,8-tetrachlorodibenzo-p-dioxin. At high doses, 3,4-dichloronitrobenzene was weakly mitogenic for ST strains TA100 and TA1538. This mutagenicity was enhanced in the presence of Aroclor 1254-induced rat liver S9 mix. The compounds 4,4'-dichloroazobenzene and 4,4'-dichloroazobenzene were mutagenic for strains TA1538, TA98, and TA100 in the presence of Aroclor 1254-induced S9 mix, the reversion rate with these compounds being related to the S9 mix composition. Negative results were obtained with liver fractions from rats pretreated with phenobarbitone or no drug. TCAB was very weakly mutagenic in the presence of Aroclor 1254-induced S9 mix. (24 Refs)

IV. INTERACTION OF DIOXINS AND DIBENZOFURANS WITH RECEPTORS AND MACROMOLECULES

89. DETECTION OF THE 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN (TCDD) RECEPTOR IN RAT LIVER BY ISOELECTRIC FOCUSING IN POLYACRYLAMIDE GELS.

Carlstedt-Duke J, Elfstrom G, Snochowski M, Hogberg B, Gustafsson JA
Dept. Chemistry, Karolinska Institutet, S-104 01 Stockholm 60, Sweden
Toxicol Lett; 2(6):365-373 1978

Isoelectric focusing in polyacrylamide gels was used to detect the 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) receptor in rat liver. Both serum and liver cytosol from young male Sprague-Dawley rats contained a dextran-coated charcoal-resistant (3H)-TCDD-binding protein, the serum-binding protein having a larger capacity than the cytosol-binding protein. The serum-binding protein focused as a sharp peak with pI 5.7 to 5.8, whereas the cytosol-binding protein focused as several peaks with variable pI's. The cytosol TCDD receptor could be completely separated from the serum binder by trypsin treatment and isoelectric focusing. The binding of (3H)-TCDD to the receptor was competed for by 2,3,7,8-tetrachlorodibenzofuran, 3-methylcholanthrene, and beta-naphthoflavone, but not by phenobarbital, pregnenolone-16alpha-carbonitrile, 17beta-estradiol, testosterone, progesterone, or dexamethasone. (14 Refs)

90. STUDIES ON THE MECHANISM OF THE CHLORINATED DIBENZO-P-DIOXINS AND RELATED COMPOUNDS (MEETING ABSTRACT).

Greenlee WF, Poland A
Univ. Rochester Sch. Medicine, Rochester, NY
The Scientific Basis for the Public Control of Environmental Health Hazards, held by the New York Academy of Sciences in New York, 21-30 June, 1978. The New York Academy of Sciences, New York, New York, 1978.

Halogenated dibenzo-dioxins such as 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) and dibenzofurans, azo- and azoxybenzenes, and biphenyls which are approx stereoisomers of TCDD, are potent inducers of the microsomal monooxygenase activity, arylhydrocarbon hydroxylase (AHH). We have isolated a cytosolic protein from liver which has the in vitro binding properties expected of the receptor for induction of AHH activity, ie the binding affinity of chlorinated aromatic hydrocarbon congeners corresponds to their potency to induce this enzyme activity. The TCDD-cytosolic binding protein complex translocates to the nucleus. Genetic evidence suggests that the receptor-ligand complex initiates not only the induction of AHH activity, but the expression of a number of structural genes. For congeners of each of the classes of halogenated aromatic compounds listed above there is an excellent correlation between their binding affinity for the cytosolic protein and their toxic potency. We propose that the initial event in the toxicity of these compounds is their binding to and sustained occupation of the cytosolic receptor. (no Refs)

91. HEPATIC NUCLEAR UPTAKE OF 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN IN INBRED MICE (MEETING ABSTRACT).

Greenlee WF, Poland A
Univ. Rochester Sch. Medicine and Dentistry, Rochester, NY, 14642

Fed Proc; 38(3,part1):425 1979

We have obtained evidence indicating that biologically specific hepatic nuclear uptake of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), a potent inducer of cytochrome P1-450 and associated monooxygenase activities, is mediated by its cytosol receptor protein. Specific hepatic nuclear uptake of [3H]TCDD in C57BL/6J mice correlated temporally with a fall in the specific binding capacity of the cytosol fraction for the inducer measured in vitro. The hepatic nuclear uptake of [3H]TCDD was 5-fold greater in C57BL/6J mice than in DBA/2J mice and was displaceable by the simultaneous administration of unlabeled TCDD, but not by inactive congeners. In vitro, the specific uptake of [3H]TCDD by hepatic nuclei from C57BL/6J mice was 10-to 15-fold greater when incubated with charged cytosol from the same strain than when incubated with heat-inactivated or trypsin-treated hepatic cytosol from C57BL/6J mice, hepatic cytosol from DBA/2J mice, or a soln of bovine serum albumin. The ability of unlabeled polycyclic aromatic hydrocarbons and halogenated aromatic congeners to compete for the specific nuclear uptake of [3H]TCDD in vitro mirrored their ability to compete with the radioligand for specific binding sites in the cytosol. (no Refs)

92. TISSUE DISTRIBUTION OF THE RECEPTOR FOR 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN IN THE RAT.

Carlstedt-Duke JM
Dept. Chemistry, Karolinska Institutet, S-104 01 Stockholm 60, Sweden

Cancer Res; 39(8):3172-3176 1979

The tissue distribution of the receptor protein for 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) in adult male Sprague-Dawley rats was determined by isoelectric focusing in polyacrylamide gel of cytosol labeled with [3H]TCDD. In order that the TCDD receptor focuses as a single sharp peak at pl 5.2, partial proteolysis of the receptor must first be carried out. The radioactivity bound to this peak was completely displaced when labeling of the cytosol was carried out in the presence of 100-fold unlabeled 2,3,7,8-tetrachlorodibenzofuran. The highest concentration of the TCDD receptor was found in thymus (25.2 femtomoles (fmol)/mg protein; n = 10) and lung cytosol (20.8 fmol/mg protein). No significant difference was seen between the concentration of the receptor in liver (13.9 fmol/mg protein) and kidney cytosol (12.5 fmol/mg protein). Low concentrations of the receptor were found in testis (3.5 fmol/mg protein), brain (2.8 fmol/mg protein), and skeletal muscle cytosol (0.3 fmol/mg protein). No receptor could be detected in the cytosol from pancreas, the adrenal glands, or ventral prostate. Ventral prostate was found to contain a different binding species for [3H]TCDD than the receptor. This binder focused at pl 4.7. It was not affected by incubation with the same concentration of trypsin used to partially degrade the TCDD receptor. Neither could the prostatic TCDD-binding protein be saturated by incubation in the presence of 100-fold unlabeled 2,3,7,8-tetrachlorodibenzofuran. (Author abstract) (29 Refs)

93. AN ESTIMATE OF THE MAXIMUM IN VIVO COVALENT BINDING OF 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN TO RAT LIVER PROTEIN, RIBOSOMAL RNA, AND DNA.

Poland A, Glover E
McArdle Lab. Cancer Res., Univ. Wisconsin, Madison, WI, 53706

Cancer Res; 39(9):3341-3344 1979

In light of the recently discovered potent carcinogenicity of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) in female rats, the in vivo covalent binding of [3H]TCDD to rat liver macromolecules was reexamined. Immature Sprague-Dawley rats, receiving [3H]TCDD (0.87 mCi/kg; specific activity, 39 Ci/millimole) concentrated 18%-64% of the total administered dose in their livers, but virtually all of this radioactivity (greater than 99.9%) was extractable. The max unextractable radioactivity was: protein, 60 picomoles (pmol) TCDD/mole (mol) of amino acid residue; ribosomal RNA, 12 pmol TCDD/mol of nucleotide residue; and DNA, 6 pmol TCDD/mol of nucleotide residue. If one assumes that this small residual amount of radioactivity represents covalent binding, this binding is four to six orders of magnitude lower than that of most chemical carcinogens, and the binding to DNA is equivalent to one molecule of TCDD per DNA, equivalent to 35 cells. The results suggest that it is unlikely that TCDD-induced oncogenesis is through a mechanism of covalent binding to DNA and somatic mutation. (29 Refs)

94. CHARACTERISATION AND REGULATION OF AN INTRACELLULAR RECEPTOR PROTEIN FOR COCARCINOGENS - A RECEPTOR REGULATING THE CHEMICAL INITIATION OF CANCER (MEETING ABSTRACT).

Carlstedt-Duke J, Gustafsson JA
Dept. Chemistry, Karolinska Institutet, Stockholm 60, Sweden

Cancer Treat Rep; 63(7):1180 1979

2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) binds to a specific intracellular receptor protein in rat liver cytosol with high affinity and low capacity (dissociation constant (Kd) = 0.6 nanoM, Bmax = 30 femtomole/mg protein). This protein, a putative receptor for cocarcinogens, can be detected and quantitated with the help of isoelectric focusing in polyacrylamide gels. Using this method, the receptor was found in high concentrations in thymus, liver, lung and kidney cytosol and in low concentrations in testis, brain and skeletal muscle cytosol in the rat. The concentrations of the receptor in liver cytosol at various ages between birth and 8 wk of age have been studied. No sexual differences were seen at any age. The max concentration of the receptor occurs at 21 days of age. Physical characterization of the liver TCDD-receptor complex demonstrated a Stokes radius of 6.6 nanometer and a sedimentation coefficient of 5.0 Svedberg units (S). The TCDD-receptor complex interacts with DNA without prior heat activation whereas the free receptor does not. (no Refs)

95. DEPENDENCE OF THE PORPHYROGENIC EFFECT OF 2,3,7,8-TETRACHLORODIBENZO(P)DIOXIN UPON INHERITANCE OF ARYL HYDROCARBON HYDROXYLASE RESPONSIVENESS.

Jones KG, Sweeney GD
Lab. Pharmacology, Natl. Inst. Environmental Health Sciences, P.O. Box 12233, Research Triangle Park, NC, 27511

Toxicol Appl Pharmacol; 53(1):42-49 1980

The hypothesis that susceptibility to porphyria depends on responsiveness to induction by 2,3,7,8-tetrachlorodibenzo(p)dioxin (TCDD) of aryl hydrocarbon

hydroxylase (AHH) (a cytochrome-P1-450 mediated hepatic microsomal monooxygenase) was studied in mice which were genetically responsive (C57BL/6J) or non-responsive (DBA/2J) to induction of AHH. Susceptibility of mice to the porphyrogenic effect of TCDD does segregate with the inheritance of the gene controlling AHH responsiveness. Either expression of the same gene is necessary for both events, or genes controlling the two events are closely linked. (22 Refs)

96. INDUCTION, INHIBITION, AND SOME ENZYMOLOGICAL PROPERTIES OF ARYL HYDROCARBON HYDROXYLASE IN FRESH MITOGEN-ACTIVATED HUMAN LYMPHOCYTES.

Gurtoo HL, Parker NB, Paigen B, Havens MB, Minowada J, Freedman HJ
Grance Cancer Drug Center, Roswell Park Memorial Inst., 666 Elm Street, Buffalo, NY, 14263
Cancer Res; 39(11):4620-4629 1979

Basal and/or polycyclic aromatic hydrocarbon (PAH)-induced aryl hydrocarbon hydroxylase (AHH) in mitogen-activated cultured lymphocytes obtained from healthy donors was studied for the specificity of induction and inhibition and of other enzymological properties. Of the 24 chemicals tested, 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), dibenz(a,h)anthracene (DBA), benz(a)anthracene (BA), 3-methylcholanthrene (3-MC), beta-naphthoflavone cholecalciferol, and DL-isoproterenol were good inducers (inducibility ratio, greater than 2.0). Other chemicals which produced effects ranging from inhibition to mild induction included 4-bromoflavone, alpha-naphthoflavone, chrysene, p,p-1,1-trichloro-2,2-bis(p-chlorophenyl)ethane, 7,12-dimethylbenzanthracene, pyrene, DL-norepinephrine, benzo(a)pyrene, lindane, nu-octylamine, testosterone, 2,5-diphenyloxazole, 17beta-estradiol, metyrapone, and phenobarbital. TCDD was the most potent inducer, followed by DBA greater than or equal to BA greater than 3-MC. Data suggest that the latter four inducers could be used interchangeably as they appear to activate the common, genetically determined factors involved in the induction of AHH. The order of potency among the inhibitors was alpha-naphthoflavone greater than beta-naphthoflavone, followed by 2-diethylaminoethyl-2,2-diphenylvalerate, metyrapone, 1,1,1,-trichloropropene oxide, and cyclohexene oxide. Depending upon the concentration used, the latter four inhibitors produced moderate inhibition to moderate stimulation; however, the inhibition pattern for the basal and the PAH-induced AHH was indistinguishable. The half-life of the enzyme during cell culture and the Km values of the AHH in uninduced and PAH-induced cells were also similar. Thus, basal and induced AHH appear to be qualitatively similar, differing only quantitatively in comparable uninduced and PAH-induced cells. (52 Refs)

97. ONTOGENY OF THE RAT HEPATIC RECEPTOR FOR 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN AND ITS ENDOCRINE INDEPENDENCE.

Carlstedt-Duke JM, Elfstrom G, Hogberg B, Gustafsson JA
Dept. Chemistry and Medical Nutrition, Karolinska Inst., S-104 01 Stockholm 60, Sweden
Cancer Res; 39(11):4653-4656 1979

The ontogeny of the 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) receptor was studied in Sprague-Dawley rats by quantitation of the receptor in liver cytosol using isoelectric focusing in polyacrylamide gel. No differences by sex in the receptor concentration were seen at any of the ages studied. Newborn, 21-day-old, and 42-day-old rats contained significantly more receptor in the liver cytosol than did 56-day-old rats. There was no significant difference in the receptor concentration in liver cytosol from 7-day-old rats compared to that from 56-day-old rats. The max receptor concentration was found in cytosol from 21-day-old rats [36.1 +-24.0 (standard deviation) femtomole/mg protein]. Adult rats (56 days old) contained the lowest concentration of receptor (13.3 +-6.3 femtomole/mg protein). The level of TCDD receptor in liver cytosol from adult rats was not significantly changed by orchiectomy, ovariectomy, adrenalectomy, or hypophysectomy. The max for TCDD receptor concentration at puberty corresponds to the reported max for the induction of aryl hydrocarbon hydroxylase activity. However, no further conclusion can as yet be drawn concerning the regulation of the TCDD receptor. (Author abstract) (20 Refs)

98. CYTOSOLIC RECEPTOR FOR AH LOCUS: EVIDENCE FOR REGULATORY GENE DYSFUNCTION IN NONRESPONSIVE CELL CULTURES CONTAINING THE RECEPTOR. (MEETING ABSTRACT).

Guenthner TM, Nebert DW
Developmental Pharmacology Branch, NICHD, NIH, Bethesda, MD 20014
Fed Proc; 36(3):648 1977

The ED50 for aryl hydrocarbon hydroxylase (AHH) induction in Hepa-1 and H-4 Reuber cell lines by 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) is 0.23-0.45 nM and the apparent Kd for TCDD binding to the cytosolic receptor is 0.5-1.0 nM; the ED50 in 'nonresponsive' HTC and VERO cell lines is 100->200 nM and the apparent Kd is 1.5-2.0 nM (Guenthner et al, Fed Proc 35: 282 (1976)). Receptors from responsive and nonresponsive cell lines have similar apparent Kd constant, intracellular concentration, and inducer specificity. Receptors from responsive cell lines differ from those in nonresponsive cell lines with respect to heat lability. During induction of AHH activity in responsive lines by 3-methylcholanthrene or benz(a)anthracene, there is a 50% increase in number of binding sites at 24 and 48 hours; no such increase occurs in the nonresponsive cell lines. Whether this increase in binding sites represents de novo synthesis, activation of preexisting inactive moieties, or decrease in degradation remains to be determined. Certain receptor-containing tissue culture cell line variants therefore possess altered receptor molecules for TCDD, as has been previously shown to be the case for receptors for steroids. These data suggest that mutants in regulatory genes - other than the gene controlling receptor content and/or affinity - are involved in the chronological sequence of events of the induction process in response to polycyclic aromatic hydrocarbons. (Author Abstract)

V. EPIDEMIOLOGIC RE-

PORTS ON THE EFFECTS OF EXPOSURE TO DIOXINS AND DIBENZOFURANS

99. HUMAN HEALTH EFFECTS FROM ACCIDENTAL RELEASE OF TETRACHLORODIBENZO-P-DIOXIN (TCDD) AT SEVESO, ITALY.

Pocchiari, F, Silano V, Zampieri A
Institute Superiore di Sanita, Rome, Italy
Ann NY Acad Sci; 320:311-320 1979

100. MORTALITY OF FOREST WORKERS EXPOSED AND UNEXPOSED TO PHENOXY ACID PREPARATIONS.

Hogstedt C, Westerlund B
Orebre, Sweden
Lakartidningen; 77(19):1828-1831 1980

Mortality and tumor incidence of 142 forest workers exposed to phenoxy acid preparations, 244 unexposed workers, and 16 foremen were investigated in an epidemiological study using payrolls from the 1950's and 1960's. The highly exposed foremen showed significantly greater incidence of tumors compared with normal values taken from the cancer registry statistics. Occupational exposure to various phenoxy acid preparations, ie amitrol, 2,4,5-T (2,4,5-trichlorophenoxyacetic acid) and its derivative, TCDD (2,3,7,8-tetrachlorodibenzo-p-dioxin), and 2,4-D (2,4-dichlorophenoxyacetic acid) resulted in malignant soft-tissue tumors. These compounds are also teratogenic and mutagenic. Aerial spraying with 2,4,5-T was implicated in miscarriages in Oregon and chromosomal damage in Vietnam. Phenoxy preparations have been used in Sweden since the early 1950's for control of vegetation. The subjects of the study were divided in three groups: exposed workers (more than 5 days exposure), foremen (highest exposed), and unexposed. Many of the 142 exposed workers had also planted DDT-treated trees. The foremen had higher mortality and tumor deaths than normal (3 to 1), while tumor deaths were lower than normal both among exposed and unexposed workers. With minimum 60 days exposure tumor mortality increased and this trend became stronger with 120 days exposure. The higher tumor deaths among the foremen might have been associated with their greater exposure to phenoxy acid preparations. It is conceivable that phenoxy acid preparations, just like vinyl chloride, increase the incidence of certain types of tumors but that their overall carcinogenicity is relatively low or moderate. (15 Refs)

101. ASSESSING HAZARDS FROM PROLONGED AND REPEATED EXPOSURE TO LOW DOSES OF TOXIC SUBSTANCES.

Barnes JM
Medical Res. Council, Toxicology Unit, Carshalton, Surrey, England
Br Med Bull; 31(3):196-200 1975

The possible long-term effects of exposure to low doses of toxic substances are discussed. In presenting an analogy with vitamins, it is suggested that while some trace substances carry out essential roles in whole-body metabolism, others may have detrimental effects. The mode of action and mode of disposal by the whole organism would then determine the danger and possible secondary effects of repeated low doses of such poisons. The need of such toxic substances to reach critical concentrations for competitive action is acknowledged. However, the specificity and reversibility of its adverse reactions in the tissues, and not the degree of water solubility, determines the safety level of repeated doses. The reaction rates also determine the nature of the pharmacological response. In evaluating the nature of the toxic injury, it is noted that the toxic effects of most organophosphorus inhibitors of cholinesterase are either immediately fatal or rapidly and totally reversible. However, delayed structural damage involving the central and peripheral nervous systems is also caused by tri-o-cresyl phosphate , suggesting a possible cumulative effect of exposure to low doses. Consideration of persistent organochlorine compounds notes the establishment of steady state body levels of DDT and dieldrin , the rapid metabolization of methoxychlor and endrin , and the accumulation of hexachloroxycyclohexane . Limited information on the mode of action of DDT and dieldrin indicate the ingestion of dietary residues has no adverse effects, as critical blood levels are not reached. In contrast to most organochlorine insecticides, data indicate that chlorinated dibenzodioxins and their toxic effects on liver cell membranes are persistent and cumulative. A dose-response of tumor formation by chemical carcinogens is suggested, and prolonged exposure is thus cautioned. Also, sensitized persons may exhibit severe and progressive responses to toxic compounds. (30 refs)

102. VIETS AND VETS FEAR HERBICIDE HEALTH EFFECTS. VIETNAMESE OFFICIAL BRINGS CONCERNS TO WASHINGTON.

Wade N
No affiliation given
Science; 204(4395):817 1979

The possibility that the (2,4,5-trichlorophenoxy)acetic acid herbicide contaminant dioxin may be carcinogenic has been raised by a Vietnamese surgeon. The incidence of liver cancer during 1974-1977 apparently increased in areas of South Vietnam that had received the bulk of the spraying, whereas the incidence in North Vietnam remained the same. Chloracne, birth defects, miscarriages, and chromosome breaks have also been observed in Vietnamese who inhabited sprayed areas. The chloracne, numbness of the digits, irritability, and other toxic reactions noted in significant numbers of Vietnam veterans may also be related to dioxin exposure in Vietnam veterans. (1 Ref)

103. DEADLY LEGACY: DIOXIN AND THE VIETNAM VETERAN.

Thomasson WA
No affiliation given
Bull At Sci; 35(5):15-19 1979

Dioxin, a contaminant of a herbicide [(2,4,5-trichlorophenoxy)acetic acid] widely used in Vietnam, apparently caused numbness and tingling in the hands and feet, depression, irritability, memory loss, and even cancer in veterans 8-12 yr after their last exposure. Some had fathered deformed children. Extremely small amounts of dioxin caused death in mice and rats, and rats fed a diet with as little as 5 parts per trillion dioxin developed tumors. The chemical also produced mutations in Salmonella and other bacteria. (13 Refs)

104. EFFECTS OF DIOXIN EXPOSURE (LETTER TO EDITOR).

Crow KD, LaPorte JR
Dept. Dermatology, Princess Margaret Hosp., Swindon SN1 4JU, England
Lancet; 2(8028):82-83 1977

Specific examples of chronic exposure of Czech workers to dioxin and dioxin plant spraying in Florida, are given by

Crow to refuse a recently published article by LaPorte. The long term effects of 2,4,5-T/2,4-D herbicide spraying in Vietnam were compared with industrial accidents involving exposure of factory workers to tetrachlordibenzo-P-dioxin in LaPorte's original article. A rebuttal is included. (19 Refs)

105. MALIGNANT LYMPHOMA OF HISTIOCYTIC TYPE AND EXPOSURE TO PHENOXYACETIC ACIDS OR CHLOROPHENOLS (LETTER TO EDITOR).

Hardell L
Dept. Oncology, Univ. Hosp., S-901 85 Umea, Sweden
Lancet; 1(8106):55-56 1979

Fourteen of 17 patients with histiocytic-type malignant lymphoma admitted to the oncology department of one hospital during a 3-mo period reported current or prior employment at a job in which exposure to phenoxyacetic acids or chlorophenols may have taken place. Eleven patients reported definite exposure to the chemicals. All but 1/11 patients were exposed to chemicals containing dibenzodioxin or dibenzofuran contaminants. (4 Refs)

106. DISPOSITION OF TETRACHLORODIBENZOFURAN IN MALE RATS (MEETING ABSTRACT).

Birnbaum LS, Decad GM, Matthews HB
NIEHS, Research Triangle Park, NC, 27709
Fed Proc; 39(3,part2):999 1980

2,3,7,8-Tetrachlorodibenzofuran (TCDF) is an extremely toxic environmental pollutant found as a contaminant in commercial polychlorinated biphenyls and pentachlorophenol mixtures. The distribution of 14C-TCDF (purity greater than 99%) was studied in 200-250 mg male Fischer 344 rats after po and iv administration. TCDF was completely absorbed at two dose levels (0.1 and 1.0 umoles/kg). The liver was the main site of TCDF accumulation, with lesser amounts being present in the adipose tissues and skin. However, within 3 days, less than 5% of the initial dose remained in the liver or fat and less than 2% remained in the skin, with no other tissues exhibiting significant amounts of radioactivity. More than 50% of the administered dose was excreted in the feces within 48 hr and greater than 90% within 5 days. Approx 3% of the dose was eliminated in the urine within 5 days. In studies of biliary excretion, 5% of the radioactivity initially administered as TCDF was excreted in the bile within 4 hr as one or more metabolites of TCDF. None of the meterial removed co-chromatographed with the parent compound. Thus, TCDF is completely absorbed, concentrated in the liver, fat and skin, metabolized, and excreted primarily by the fecal route. (no Refs)

VI. ENVIRONMENTAL OCCURRENCE, PUBLIC HEALTH ISSUES AND REGULATIONS CONCERNING DIOXINS AND DIBENZOFURANS

107. ENVIRONMENTAL INTOXICANTS AND THEIR FUNDAMENTAL INTERACTIONS.

Eisinger J, Blumberg WE
Bell Labs., Murray Hill, NJ, 07974
Q Rev Biophys; 11(4):429-437 1978

Diseases of environmental origin and their role in an industrial society are reviewed. The manifestations of adverse environments can be divided into two groups: (1) widely distributed environmental conditions (ie, asbestos, aflatoxin, zeolite, and polycyclic aromatic hydrocarbons and (2) environmental health disasters that result from heavy exposure of a localized population to a toxic environment (ie, lead, methyl mercury, and chlorinated dibenzo-p-dioxins). The first group is generally associated with a low incidence of disease. The related health problems are difficult to trace and are often unrecognized. (24 Refs)

108. DANGERS OF T.C.D.D. (LETTER TO EDITOR).

Dewse CD
Cytogenetics Unit, Nuffield Wing, Sch. Medicine, P.O. Box 147, Liverpool L69 3BX, England
Lancet; 2(7981):363 1976

The full import of the accidental release of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) in the Seveso region of Italy has not been publicized in the press. An immediate full-scale evacuation of the area was warranted. TCDD is 30,000 times more potent an inducer of aryl hydrocarbon hydroxylase (AHH) than 3-methylcholanthrene in rat liver and is 40 to 60 times more potent as an inducer of AHH in cultured human lymphocytes. AHH is strongly implicated in chemical carcinogenesis in that many chemically non-reactive carcinogens must be metabolized by cellular enzymes to produce biological effects such as carcinogenesis. Continuous exposure of a population to such a potent inducer of an enzyme which catalyzes these reactions carries evident risks. (13 refs)

109. YOU ARE WHAT YOU EAT.

Nisbet IC
Massachusetts Audubon Society, MA
Technol Rev; 79(7):5,16-17 1977

The environmental, economic, and health effects of eating large amounts of meat are discussed. Several potentially carcinogenic chemicals are concentrated in animal fats, including residues of soil insecticides (dieldrin, heptachlor, chlordane); residues of synthetic hormones such as diethylstilbestrol, used to promote wt gain in cattle; and dioxins (toxic contaminants of range herbicides). Recent evidence suggests an association between current patterns of cancer incidence and meat consumption. The statistical association is becoming steadily clearer, but definite evidence for a cause-and-effect relationship is still weak. It is not clear whether the causative agent(s) is animal fats, the meats themselves, diets low in fibers, preservatives, contaminants, or other factors associated with Western diets. (no Refs)

110. POLYCHLORINATED DIBENZOFURANS (PCDFS) FOUND IN YUSHO OIL AND IN USED JAPANESE PCB.

Buser HR, Rappe C, Gara A
Swiss Federal Res. Station, CH-8820 Wadenswil, Switzerland
Chemosphere; 7(5):439-449 1978

The results of an analysis of the polychlorinated dibenzofurans (PCDFs) present in Japanese Yusho oil (rice oil) and in polyclorinated biphenyl (PCB) used for 2 yr in Japan in a heat exchanger are reported. A simplified clean-up procedure and high resolution gas chromatography and mass spectrometry were used for the analysis. The Yusho oil was adsorbed onto a silica column and the PCBs and PCDFs eluted with hexane. Further purification of the extract was done by chromatography on alumina to separate PCBs from PCDFs and other chlorinated trycyclic aromatic compounds. The clean-up procedure for the used PCB was similar, except that the silica column was replaced by an alumina column. Based on mass fragmentography data, the amounts of tri-, tetra-, penta-, and hexa-PCDFs in the Yusho oil were 0.15, 1.4, 2.5, and 1.6 microg/g respectively and in used PCB were 4.2, 4.5, 5.5, and 1.4 microg/g, respectively. Yusho oil contained less tri-CDFs, the major isomers in the two samples were the same. The major isomer in the tetra-CDFs from both samples was the extremely toxic 2,3,7,8-tetra-CDF. The major isomers of the penta- and hexa-CDFs from both samples were very similar with one exception. These results show a similarity between the PCDF isomers present in the Yusho oil and in the used Japanese PCB. The possible relationship between the isomers present to Yusho disease is discussed. (15 Refs)

111. AMBIENT WATER QUALITY CRITERIA: 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN.

Environmental Protection Agency
Criteria and Standards Div., Environmental Protection Agency, Washington, DC
Ambient Water Quality Criteria: 2,3,7,8-Tetrachlorodibenzo-p-Dioxin. Available Through National Technical Information Service, Springfield, Va., as PB-292 442/1GA:, 64 pp., 1978.

Section 304(a) of the Clean Water Act (33 US Congress 1314(a)), requires Environmental Protection Agency to publish and periodically update water quality criteria. These criteria are to reflect the latest scientific knowledge on the identifiable effects of pollutants on public health and welfare, aquatic life, and recreation. This report presents water quality criteria for 2,3,7,8-tetrachlorodibenzo-p-dioxin. It presents concentration criteria for the protection of fresh water and saltwater aquatic life. It presents 'safe' concentrations for humans, and in the case of suspect or proven carcinogens, gives various levels of incremental cancer risk. A section 304(a) water quality criterion is a qualitative or quantitative estimate of the concentration of a water constituent or pollutant in ambient waters which, when not exceeded, will ensure a water quality sufficient to protect a specified water use. Under the Act a criterion is a scientific entity, based solely on data and scientific judgement. It does not reflect considerations of economic or technological feasibility nor is it a water quality standard and in itself has no regulatory effect. (Author abstract) (no Refs)

SUBJECT INDEX

ABSTRACT)./ INDUCTION OF 3-ACETYLAMINOFLUORENE (
UCIBLE N-HYDROXYLATION OF 3-ACETYLAMINOFLUORENE AND
OF FOREST WORKERS EXPOSED AND UNEXPOSED TO PHENOXY
A OF HISTIOCYTIC TYPE AND EXPOSURE TO PHENOXYACETIC
TION OF HAMSTER PANCREAS./
METABOLIC
ENZO-P-DIOXIN ON GLUCURONIDE CONJUGATION OF VARIOUS
MOUSE TUMORS IN MICE GENETICALLY 'NONRESPONSIVE' AT
IVE CELL CULTURES CONTAIN/ CYTOSOLIC RECEPTOR FOR
CYTOCHROME P-448 AND ARYL HYDROCARBON HYDROXYLASE (
CHLORODIBENZO-P-DIOXIN INDUCIBLE GENOME/ RAT LIVER
COMPARISON OF PHENOBARBITAL- AND CARCINOGEN-INDUCED
XIN./
GENETIC EFFECTS OF CHLORINATED
,8-TETRACHLORODIBENZO-P-DIOXIN (TCDD) IN LABORATORY
2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN: POTENT
WO-STAGE SYSTEM OF MOUSE SKIN TUMORIGENESIS: POTENT
ON BENZO(A)PYRENE AND 7,12-DIMETHYLBENZ(A)ANTHR/
Y OF 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN (TCDD) AND
RCINOGENESIS IN RATS (MEETING / DIBENZOFURAN-FREE
S OF 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN (TCDD) AND
UDP-GLUCURONOSYLTRANSFERASE INDUCTION BY POLYCYCLIC
RYL HYDROCARBON HYDROXYLASE INDUCTION BY POLYCYCLIC
DIOXIN IN MICE GENETICALLY 'NONRESPONSIVE' TO OTHER
LUORENE AND ACETAMINO/ GENETIC DIFFERENCES IN THE
THE INTESTINE AND LIV/ EFFECTS OF POLYHALOGENATED
TOXICOPATHOLOGY CHARACTERISTICS OF THE HALOGENATED
RATORY STUDIES ON THE IMMUNE EFFECTS OF HALOGENATED
2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN INDUCTION OF
IN (TCDD) INDUCED SYNTHESIS OF CYTOCHROME P-448 AND
BY PHENOBARBITAL/ TIME COURSE OF THE INDUCTION OF
7,8-TETRACHLORODIBENZO(P)DIOXIN UPON INHERITANCE OF
UCED-NAD(P)-MENADIONE OXIDOREDUCTASE AND MICROSOMAL
INDUCTION, INHIBITION, AND BIOLOGICAL PROPERTIES OF
XIN: EVIDENCE FOR A RECEPT/ GENETIC EXPRESSION OF
SE ACTIVITIES AND CYTOCHRO/ GENETIC EXPRESSION OF
YMYLCHOLANTHRENE / RELATIONSHIP BETWEEN LEVELS OF
MPOUNDS: EVIDENCE FOR STA/ CYTOSOLIC RECEPTOR FOR
ON OF MICROSOMAL ELECTRON TRANSPORT ASSOCIATED WITH
UTATION IN NONRESPONSI/ THE GENETIC EXPRESSION OF
N, INHIBITION, AND SOME ENZYMOLOGICAL PROPERTIES OF
O DIBENZO-P-DIOXINS (MEETING ABSTRACT)./
LIC AROMATIC COMPOUNDS IN MICE. CO-SEGREGATION WITH
OCARCINOGENS TO MUTAGENS FOR SALMONELLA TYPHIMURIUM
GENETIC EFFECTS OF CHLORINATED ANILINES AND
S OF ARYL HYDROCARBON HYDROXYLASE IN A STABLE HUMAN
8-TETRACHLORODIBEN/ TRANSPLACENTAL STIMULATION OF
C EFFECTS OF 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN ON
EFFECTS OF POLYHALOGENATED AROMATIC HYDROCARBONS ON
TATIVE AND QUALITATIVE CHANGES IN THE METABOLISM OF
NDS IN MICE. CO-SEGREGATION WITH ARYL HYDROCARBON
OF CYTOCHROME P-450 FORMS IN 3-AMINOBANTHRACENE AND
VITY AND SUSCEPTIBILITY TO 3-METHYLCHOLANTHRENE AND
EIN./ AN ESTIMATE OF THE MAXIMUM IN VIVO COVALENT
RACENE TUMOR INITIATION AND ITS RELATIONSHIP TO DNA
CARCINOGENESIS
WITH DIFFERENT 2,3,7,8-TETRACHLOROD/ CARCINOGENIC

E HUMAN B-LYMPHOCYTE / INDUCTION, INHIBITION, AND
(TCB). A COMPONENT OF CARCINOGENIC POLYCHLORINATED
COMPARATIVE TOXICITY OF POLYCHLORINATED
KING, POLYBROMINATED BIPHENYLS, AND POLYCHLORINATED
WITH CHLORINATED DIBENZO-P-DIOXINS, POLYBROMINATED
TRANSPLACENTAL STIMULATION OF BENZO(A)PYRENE (
HROME-P448-ASSOCIATED ENZYMES: DETECTION BY IN VIVO
RESEARCH RELATED TO THE HERBICIDE
INDUCTION OF 3-ACETYLAMINOFLUORENE (AAF) N- AND
- A RECEPTOR REGULATING THE CHEMICAL INITIATION OF
TO 3-METHYLCHOLANTHRENE AND BENZO A PYRENE-INDUCED
CTION BY IN VIVO BREATH ANALYSIS (MEETING ABSTR/
-P-DIOXIN./ TRANSPLACENTAL INDUCTION OF
COMPARISON OF PHENOBARBITAL- AND
D CHEMICALS./
AROCHLOR 1254 IN THE TWO-STAGE SYSTEM OF MOUSE SKIN

ORGANIC COMPOUNDS./ THE
HANOL (TCPE) WITH DIFFERENT 2,3,7,8-TETRACHLORO/
3,4,3',4'-TETRACHLOROBIPHENYL (TCB). A COMPONENT OF
OL CONTAINING DIOXIN AND OF PURE DIOXIN IN SWIS/
BIOASSAY OF DIBENZO-P-DIOXIN FOR POSSIBLE
D TO THE HERBICIDE SILVEX, ESPECIALLY FOR POSSIBLE
IDENTIFYING
BENZO-P-DIOXIN: POTENT ANTICARCINOGENIC ACTIVITY IN
TRUCTURAL AND REGULATORY VARIANTS AMONG ESTABLISHED
RANSFERASE ACTIVITY IN THE REUBER H-4-II-E HEPATOMA
CE FOR REGULATORY GENE DYSFUNCTION IN NONRESPONSIVE
CTIVITY IN THE REUBER HEPATOMA H-4-II-E ESTABLISHED
KERATINIZATION OF MOUSE TERATOMA
ROCARBON HYDROXYLASE IN A STABLE HUMAN B-LYMPHOCYTE
RE TO DEMONSTRATE TOXICITY IN TWENTY-THREE CULTURED
YPE FOR COCARCINOGENS - A RECEPTOR REGULATING /
STRAIN FOR COCARCINOGENS - A RECEPTOR REGULATING THE
GENETIC EFFECTS OF
COMPARATIVE TOXICOLOGY OF

AAF) N- AND C-HYDROXYLATION IN ISOLATED RAT HEPATOCYTES (MEETING
ACETAMINOPHEN-PRODUCED HEPATOTOXICITY IN MICE / GENETIC DIFFERE
ACID PREPARATIONS / MORTALITY
ACIDS OR CHLOROPHENOLS (LETTER TO EDITOR) / MALIGNANT LYMPHON
ACTIVATION OF NITROGARENES TO MUTAGENS BY POSTMITOCHONDRIAL FRAC
ACTIVATION/DEACTIVATION REACTIONS DURING PERINATAL DEVELOPMENT
ADLYCODES. STUDIES IN WISTAR AND GUNN RATS / DIFFERENT EFFECT O
AH LOCUS: / 2,3,7,8,-TETRACHLORODIBENZO-P-DIOXIN AS COCARCINOGEN
AH LOCUS: EVIDENCE FOR REGULATORY GENE DYSFUNCTION IN NONRESPONS
AHH) ACTIVITY IN FEMALE RAT LIVER (MEETING ABSTRACT) / 2,3,7,8-
ALDEHYDE DEHYDROGENASE--IMMUNOCHEMICAL IDENTITY OF 2,3,7,8-TETRA
ALDEHYDE DEHYDROGENASES IN THE RAT /
AMBIENT WATER QUALITY CRITERIA: 2,3,7,8-TETRACHLORODIBENZO-P-DIO
ANILINES AND AZOBENZENES ON SALMONELLA TYPHIMURIUM
ANIMALS / LONG-TERM TOXICOLOGIC STUDIES OF 2,3,7
ANTICARCINOGENIC ACTIVITY IN CD-1 MICE
ANTICARCINOGENIC EFFECTS / STUDIES WITH CHLORINATED DIBENZO-P-D
ANTICARCINOGENIC EFFECTS OF 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN
AROCHLOR 1254 IN THE TWO-STAGE SYSTEM OF MOUSE SKIN CARCINOGENES
AROCLOR 1254 AS A PROMOTER OF DIETHYLNITROSAMINE (DENA) HEPATOCA
AROCLOR 1254 ON 7,12-DIMETHYLBENZ A ANTHRACENE METABOLISM AND TU
AROMATIC COMPOUNDS IN MICE. CO-SEGREGATION WITH ARYL HYDROCARBON
AROMATIC COMPOUNDS. EVIDENCE FOR STRUCTURAL AND REGULATORY VARIA
AROMATIC HYDROCARBONS. / GENETIC EXPRESSION OF ARYL HYDROCARBON
AROMATIC HYDROCARBON-INDUCIBLE N-HYDROXYLATION OF 3-ACETYLAMINOF
AROMATIC HYDROCARBONS ON BENZO(A)PYRENE HYDROXYLASE ACTIVITY IN
AROMATICS (MEETING ABSTRACT)
AROMATICS / LABO
ARYL HYDROCARBON HYDROXYLASE IN FEMALE RAT LIVER. EVIDENCE FOR G
ARYL HYDROCARBON HYDROXYLASE (ANH) ACTIVITY IN FEMALE RAT LIVER
ARYL HYDROCARBON HYDROXYLASE IN RAT LIVER NUCLEI AND MICROSOMES
ARYL HYDROCARBON HYDROXYLASE RESPONSIVENESS. / DEPENDENCE OF THE
ARYL HYDROCARBON HYDROXYLASE IN THE MOUSE. / GENETIC DIFFERENCES
ARYL HYDROCARBON HYDROXYLASE IN A STABLE HUMAN B-LYMPHOCYTE CELL
ARYL HYDROCARBON HYDROXYLASE BY 2,3,7,8-TETRACHLORODIBENZO-P-DIO
ARYL HYDROCARBON HYDROXYLASE ACTIVITY. INDUCTION OF MONOOXYGENA
ARYL HYDROCARBON HYDROXYLASE ACTIVITY AND SUSCEPTIBILITY TO 3-ME
ARYL HYDROCARBON HYDROXYLASE INDUCTION BY POLYCYCLIC AROMATIC CO
ARYL HYDROCARBON HYDROXYLASE INDUCTION IN MICE. / GENETIC EXPRES
ARYL HYDROCARBON HYDROXYLASE ACTIVITY: EVIDENCE FOR A RECEPTOR M
ARYL HYDROCARBON HYDROXYLASE IN FRESH MITOGEN-ACTIVATED HUMAN LY
ARYL HYDROCARBON HYDROXYLASE ACTIVITY OF TWENTY-THREE HALOGENATE
ARYL HYDROCARBON (BENZO(A)PYRENE) HYDROXYLASE INDUCTION / SWEET
AUXOTROPHS. / EFFECTS OF PRETREATMENT WITH 2,3,7,8-TETRACHLORODI
AZOBENZENES ON SALMONELLA TYPHIMURIUM
B-LYMPHOCYTE CELL LINE, RPMI-1788 / INDUCTION, INHIBITION, AND
BENZO(A)PYRENE (BP) METABOLISM IN EXTRAHEPATIC TISSUES BY 2,3,7,
BENZO(A)PYRENE AND 7,12-DIMETHYLBENZ(A)ANTHRACENE TUMOR INITIATI
BENZO(A)PYRENE HYDROXYLASE ACTIVITY IN THE INTESTINE AND LIVER
BENZO(A)PYRENE IN RAT TISSUES AFTER INTRAGASTRIC ADMINISTRATION
BENZO(A)PYRENE HYDROXYLASE INDUCTION / GENETIC REGULATION OF U
BENZO ALPHA PYRENE MUTAGENESIS (MEETING ABSTRACT) / THE ROLE
BENZO A PYRENE-INDUCED CANCERS IN INBRED STRAINS OF MICE / RELA
BINDING OF 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN TO RAT LIVER PROT
BINDING / ANTICARCINOGENIC EFFECTS OF 2,3,7,8-TETRACHLORODIBENZ
BIOASSAY OF CHLORINATED DIBENZODIOXINS AND RELATED CHEMICALS
BIOASSAY OF DIBENZO-P-DIOXIN FOR POSSIBLE CARCINOGENICITY
BIOASSAY OF THE HERBICIDE, 2,4,5-TRICHLOROPHENOXYETHANOL (TCPE)

BIOLOGICAL PROPERTIES OF ARYL HYDROCARBON HYDROXYLASE IN A STABL
BIPHENYL MIXTURES (MEETING ABSTRACT) / EFFECTS OF MICROSOMAL ST
BIPHENYLS AND DIBENZOFURANS IN RATS
BIPHENYLS IN A TWO-STAGE SYSTEM OF MOUSE SKIN TUMORIGENESIS: POT
BIPHENYLS, AND POLYCHLORINATED BIPHENYLS IN A TWO-STAGE SYSTEM O
BP) METABOLISM IN EXTRAHEPATIC TISSUES BY 2,3,7,8-TETRACHLORODIB
BREATH ANALYSIS (MEETING ABSTRACT) / CARCINOGEN INDUCTION OF CY
BUVINOL, ESPECIALLY FOR POSSIBLE CARCINOGENICITY
C-HYDROXYLATION IN ISOLATED RAT HEPATOCYTES (MEETING ABSTRACT)
CANCER (MEETING ABSTRACT) / CHARACTERISATION AND REGULATION OF
CANCERS IN INBRED STRAINS OF MICE / RELATIONSHIP BETWEEN LEVELS
CARCINOGEN INDUCTION OF CYTOCHROME-P448-ASSOCIATED ENZYMES: DETE
CARCINOGEN-HYDROXYLATING SYSTEMS WITH 2,3,7,8-TETRACHLORODIBENZO
CARCINOGEN-INDUCED ALDEHYDE DEHYDROGENASES IN THE RAT
CARCINOGENESIS BIOASSAY OF CHLORINATED DIBENZODIOXINS AND RELATE
CARCINOGENESIS / TUMOR-INITIATING ABILITY OF 2,3,7,8-TETRACHLOR
CARCINOGENIC ACTIVITY OF ANALOGUES OF P-DIMETHYLAMINOAZOBENZENE
CARCINOGENIC AND OTHER CHRONIC EFFECTS OF PERSISTENT HALOGENATED
CARCINOGENIC BIOASSAY OF THE HERBICIDE, 2,4,5-TRICHLOROPHENOXYET
CARCINOGENIC POLYCHLORINATED BIPHENYL MIXTURES (MEETING ABSTRACT
CARCINOGENICITY TESTING OF HERBICIDE 2,4,5-TRICHLOROPHENOXYETHAN
CARCINOGENICITY
CARCINOGENICITY / RESEARCH RELATE
CARCINOGENS
CD-1 MICE / 2,3,7,8-TETRACHLORODI
CELL CULTURE LINES. / CYTOSOLIC RECEPTOR FOR ARYL HYDROCARBON HY
CELL CULTURE / INDUCTION OF UDP-GLUCURONOSYLT
CELL CULTURES CONTAINING THE RECEPTOR (MEETING ABSTRACT)
CELL LINE (MEETING ABSTRACT). / STUDIES ON THE REQUIREMENTS FOR
CELL LINE RH PRODUCED BY 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN
CELL LINE, RPMI-1788. / INDUCTION, INHIBITION, AND BIOLOGICAL PR
CELL TYPES / 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN. FAILU
CHARACTERISATION AND REGULATION OF AN INTRACELLULAR RECEPTOR PRO
CHEMICAL INITIATION OF CANCER (MEETING ABSTRACT). / CHARACTERISA
CHLORINATED ANILINES AND AZOBENZENES ON SALMONELLA TYPHIMURIUM
CHLORINATED COMPOUNDS ON MAMMALIAN SPECIES.

32 YCHLORINATED BIPHENYLS IN A TWO-STA/ STUDIES WITH CHLORINATED DIBENZO-P-DIOXINS, POLYBROMINATED BIPHENYLS, AND POL
30 A REVIEW OF THE GENETIC TOXICOLOGY OF CHLORINATED DIBENZO-P-DIOXINS.
90 TRACT)./ STUDIES ON THE MECHANISM OF THE CHLORINATED DIBENZO-P-DIOXINS AND RELATED COMPOUNDS (MEETING ABS
2 CHLORINATED DIBENZODIOXINS.
3 CARCINOGENESIS BIOASSAY OF CHLORINATED DIBENZODIOXINS AND RELATED CHEMICALS.
105 IOCYTIC TYPE AND EXPOSURE TO PHENOXYACETIC ACIDS OR CHLOROPHENOLS (LETTER TO EDITOR). / MALIGNANT LYMPHOMA OF HIST
87 ETING ABSTRA/ STUDIES ON THE INDUCTION OF SISTER CHROMATID EXCHANGE IN HUMAN FIBROBLASTS BY DIETHYLSTILBOESTROL IN
19 YNE CARCINOGENIC AND OTHER CHRONIC EFFECTS OF PERSISTENT HALOGENATED ORGANIC COMPOUNDS.
6 IBENZO-P-DIOXIN IN RATS./ RESULTS OF A TWO-YEAR CHRONIC TOXICITY AND ONCOGENICITY STUDY OF 2,3,7,8,-TETRACHLORDD
39 (MEETING ABSTRACT)./ CHRONIC TOXICITY OF 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN IN RATS.
70 INDUCTION BY POLYCYCLIC AROMATIC COMPOUNDS IN MICE. CO-SEGREGATION WITH ARYL HYDROCARBON BENZO(A)PYRENE HYDROXYLAS
25 TUMORS / 2,3,7,8,-TETRACHLORODIBENZO-P-DIOXIN AS COCARCINOGEN CAUSING 3-METHYLCHOLANTHRENE-INITIATED SUBCUTANEOUS
72 REGULATION OF AN INTRACELLULAR RECEPTOR PROTEIN FOR CO-CARCINOGENS - A RECEPTOR REGULATING THE CHEMICAL INITIATION OF
39 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN ON GLUCURONIDE CONJUGATION OF VARIOUS AGLYCONES. STUDIES IN WISTAR AND SUMN RAT
93 EFFECTS OF ENVIRONMENTAL CONTAMINANTS ON THE IMMUNE SYSTEM.
93 IVER PROTEIN./ AN ESTIMATE OF THE MAXIMUM IN VIVO COVALENT BINDING OF 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN TO RAT L
78 URAL AND REGULATORY VARIANTS AMONG ESTABLISHED CELL CULTURE LINES. / CYTOSOLIC RECEPTOR FOR ARYL HYDROCARBON HYDROXY
82 ERASE ACTIVITY IN THE REUBER H-4-II-E HEPATOMA CELL CULTURE. / INDUCTION OF UDP-GLUCURONOSYLTRANSF
85 IN FAILURE TO DEMONSTRATE TOXICITY IN TWENTY-THREE CULTURED CELL TYPES. / 2,3,7,8-TETRACHLORODIBENZO-P-DIOX
98 R REGULATORY GENE DYSFUNCTION IN NONRESPONSIVE CELL CULTURES CONTAINING THE RECEPTOR. (MEETING ABSTRACT). / CYTOSOL
98 ACHLORODIBENZO-P-DIOXIN (TCDD) INDUCED SYNTHESIS OF CYTOCHROME P-448 AND ARYL HYDROCARBON HYDROXYLASE (AHH) ACTIVITY
44 FEMALE RAT LIVER. EVIDENCE FOR DE NOVO SYNTHESIS OF CYTOCHROME P-448. / 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN INDUCTIO
47 DEPRESSION OF GUINEA-PIG TESTICULAR MICROSOMAL CYTOCHROME P-450 CONTENT BY 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN
46 NE MUTAGENESIS (MEETING ABSTRACT)./ THE ROLE OF CYTOCHROME P-450 FORMS IN 3-AMINOANTHRACENE AND BENZO ALPHA PYRE

45 TS BY 2,3,7,8-TETRAC/ IDENTIFICATION OF THE MAJOR CYTOCHROME P-450 FORM TRANSPLACENTALLY INDUCED IN NEONATAL RABB/
48 ,3,7,8-TETRACHLORODIBENZO-P-DI/ MULTIPLE FORMS OF CYTOCHROME P-450 FROM LIVER MICROSOMES OF RABBITS TREATED WITH 2
43 ,3,7,8-TETRACHLORODIB/ RESOLUTION OF TWO FORMS OF CYTOCHROME P-450 FROM LIVER MICROSOMES OF RABBITS TREATED WITH 2
91 NO MOUSE LIVER FOR TEMPORAL CONTROL OF TWO FORMS OF CYTOCHROME P-450 INDUCIBLE BY 2,3,7,8-TETRACHLORODIBENZO-P-DIOX
85 CTIVITY INDUCTION OF MONOOXYGENASE ACTIVITIES AND CYTOCHROME P1-450 FORMATION BY 2,3,7,8-TETRACHLORODIBENZO-P-DIOX
49 ANALYSIS (MEETING ABSTRA/ CARCINOGEN INDUCTION OF CYTOCHROME-P448-ASSOCIATED ENZYMES. DETECTION BY IN VIVO BREATH
93 RYL HYDROCAR/ GENETIC DIFFERENCES IN INDUCTION OF CYTOSOL REDUCED-NAD(P)-MENADIONE OXIDOREDUCTASE AND MICROSOMAL A
93 DN GLUTATHIONE S-TRANSFERASE ACTIVITY OF RAT LIVER CYTOSOL. / THE INFLUENCE OF PHENOBARBITAL, 3-METHYLCHOLANTHRENE,
98 SFUNCTION IN NONRESPONSIVE CELL CULTURES CONTAI/ CYTOSOLIC RECEPTOR FOR AN LOCUS. EVIDENCE FOR REGULATORY GENE DY
78 POLYCYCLIC AROMATIC COMPOUNDS. EVIDENCE FOR ST/ CYTOSOLIC RECEPTOR FOR ARYL HYDROCARBON HYDROXYLASE INDUCTION BY
81 ENZO-P-DIOXIN INDUCIBLE NORMA/ RAT LIVER ALDEHYDE DEHYDROGENASE--IMMUNOCHEMICAL IDENTITY OF 2,3,7,8-TETRACHLORODIB
73 N OF PHENOBARBITAL- AND CARCINOGEN-INDUCED ALDEHYDE DEHYDROGENASES IN THE RAT. / COMPARISO
64 ACTIVATION/DEACTIVATION REACTIONS DURING PERINATAL DEVELOPMENT. / METABOLIC
4 BIOASSAY OF DIBENZO-P-DIOXIN FOR POSSIBLE CARCINOGENICITY.
80 DN HYDROXYLASE ACTIVITY OF TWENTY-THREE HALOGENATED DIBENZO-P-DIOXINS (MEETING ABSTRACT). / ARYL HYDROCARB
90 STUDIES ON THE MECHANISM OF THE CHLORINATED DIBENZO-P-DIOXINS AND RELATED COMPOUNDS (MEETING ABSTRACT).
23 BIPHENYLS IN A TWO-STA/ STUDIES WITH CHLORINATED DIBENZO-P-DIOXINS, POLYBROMINATED BIPHENYLS, AND POLYCHLORINATED
30 A REVIEW OF THE GENETIC TOXICOLOGY OF CHLORINATED DIBENZO-P-DIOXINS.
10 POLYCHLORINATED DIBENZODIOXINS AND DIBENZOFURANS--COMPOUNDS OF CURRENT INTEREST.
3 CARCINOGENESIS BIOASSAY OF CHLORINATED DIBENZODIOXINS AND RELATED CHEMICALS.
2 CHLORINATED DIBENZODIOXINS. / CO
27 NE (DENA) HEPATOCARCINOGENESIS IN RATS (MEETING/ DIBENZOFURAN-FREE AROCLOR 1254 AS A PROMOTER OF DIETHYLNITROSAMI
110 S./ POLYCHLORINATED DIBENZOFURANS (PCDFS) FOUND IN YUSHO OIL AND IN USED JAPANESE PC
32 MPARATIVE TOXICITY OF POLYCHLORINATED BIPHENYLS AND DIBENZOFURANS IN RATS. / CO
10 POLYCHLORINATED DIBENZODIOXINS AND DIBENZOFURANS--COMPOUNDS OF CURRENT INTEREST.
56 LCHOLANTHRENE, 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN, DIBENZOFURANS AND RELATED CHEMICALS.
27 DIBENZOFURAN-FREE AROCLOR 1254 AS A PROMOTER OF DIETHYLNITROSAMINE (DENA) HEPATOCARCINOGENESIS IN RATS (MEETING
28 CHLORODIBENZO-P-DIOXIN OF HEPATOCARCINOGENESIS FROM DIETHYLNITROSAMINE. / QUANTITATIVE EVALUATION OF THE PROMOTION B
87 F SISTER CHROMATID EXCHANGE IN HUMAN FIBROBLASTS BY DIETHYLSTILBOESTROL (MEETING ABSTRACT). / STUDIES ON THE INDUCTIO
14 HERBICIDE 2,4,5-TRICHLOROPHENOXYETHANOL CONTAINING DIOXIN AND OF PURE DIOXIN AND OF PURE DIOXIN IN SWISS MICE. / CARCINOGENICITY TESTI
103 DEADLY LEGACY. DIOXIN AND THE VIETNAM VETERAN.
104 EFFECTS OF DIOXIN EXPOSURE (LETTER TO EDITOR).
14 (CHLOROPHENOXYETHANOL CONTAINING DIOXIN AND OF PURE DIOXIN IN SWISS MICE. / CARCINOGENIC BIOASSAY OF THE HE
13 (TH DIFFERENT 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN (DIOXIN) CONTENT IN SWISS MICE. / CARCINOGENICITY TESTING OF HERBICIDE 2,4
75 THE RAT./ DISPOSITION AND EXCRETION OF 2,3,7,8-TETRACHLORODIBENZOFURAN IN
74 TRACT)./ DISPOSITION OF TETRACHLORODIBENZOFURAN IN MALE RATS (MEETING ABS
106 TRACT)./ DISPOSITION OF TETRACHLORODIBENZOFURAN IN MALE RATS (MEETING ABS
23 ANTHRACENE TUMOR INITIATION AND ITS RELATIONSHIP TO DNA BINDING. / ANTICARCINOGENIC EFFECTS OF 2,3,7,8-TETRACHLORODI
93 O-P-DIOXIN TO RAT LIVER PROTEIN, RIBOSOMAL RNA, AND DNA. / AN ESTIMATE OF THE MAXIMUM IN VIVO COVALENT BINDING OF 2,
101 HAZARDS FROM PROLONGED AND REPEATED EXPOSURE TO LOW DOSES OF TOXIC SUBSTANCES. / ASSESSING
53 INDUCTION OF DRUG METABOLIZING ENZYMES IN DIFFERENT RAT TISSUES BY TCDD.
71 INDUCTION OF DT-DIAPHORASE BY 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN.
98 RECEPTOR FOR AN LOCUS. EVIDENCE FOR REGULATORY GENE DYSFUNCTION IN NONRESPONSIVE CELL CULTURES CONTAINING THE RECEPT
98 INDUCTION IN MI/ GENETIC EXPRESSION OF MICROSOMAL ELECTRON TRANSPORT ASSOCIATED WITH ARYL HYDROCARBON HYDROXYLASE
97 TOR FOR 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN AND ITS ENDOCRINE INDEPENDENCE. / ONTOGENY OF THE RAT HEPATIC RECEP
24 ASSAY/ LACK OF TUMOR-PROMOTING ABILITY OF CERTAIN ENVIRONMENTAL CHEMICALS IN A TWO-STAGE MOUSE SKIN TUMORIGENESIS
38 EFFECTS OF ENVIRONMENTAL CONTAMINANTS ON THE IMMUNE SYSTEM.
107 ENVIRONMENTAL INTOXICANTS AND THEIR FUNDAMENTAL INTERACTIONS.
53 INDUCTION OF DRUG METABOLIZING ENZYMES IN DIFFERENT RAT TISSUES BY TCDD.
48 CARCINOGEN INDUCTION OF CYTOCHROME-P448-ASSOCIATED ENZYMES. DETECTION BY IN VIVO BREATH ANALYSIS (MEETING ABSTRACT)
88 H MITOGEN-ACTIVA/ INDUCTION, INHIBITION, AND SOME ENZYMOLOGICAL PROPERTIES OF ARYL HYDROCARBON HYDROXYLASE IN FRES
31 IN IN THE RAT. MORPHOLOGICAL, ULTRASTRUCTURAL, AND ENZYMOLOGICAL STUDY OF THE LIVER. / SHORT-TERM TOXICITY OF 2,3,7
78 DISPOSITION AND EXCRETION OF 2,3,7,8-TETRACHLORODIBENZOFURAN IN THE RAT.
100 MORTALITY OF FOREST WORKERS EXPOSED AND UNEXPOSED TO PHENOXY ACID PREPARATIONS.
8 INCREASED INCIDENCE OF NEOPLASMS IN RATS EXPOSED TO 2,3,7,8-TETRACHLORODIBENZO-AND-DIOXIN.
7 INCREASED INCIDENCE OF NEOPLASMS IN RATS EXPOSED TO LOW LEVELS OF 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN.
104 EFFECTS OF DIOXIN EXPOSURE (LETTER TO EDITOR).
101 ASSESSING HAZARDS FROM PROLONGED AND REPEATED EXPOSURE TO LOW DOSES OF TOXIC SUBSTANCES.
105 OR). / MALIGNANT LYMPHOMA OF HISTIOCYTIC TYPE AND EXPOSURE TO PHENOXYACETIC ACIDS OR CHLOROPHENOLS (LETTER TO EDIT
85 OF MONOOXYGENASE ACTIVITIES AND CYTOCHRO/ GENETIC EXPRESSION OF ARYL HYDROCARBON HYDROXYLASE ACTIVITY. INDUCTION

87 ODIBENZO-P-DIOXIN. EVIDENCE FOR A RECEPT/ GENETIC EXPRESSION OF ARYL HYDROCARBON HYDROXYLASE BY 2,3,7,8-TETRACHLOR
88 R A RECEPTOR MUTATION IN NONRESPONSI/ THE GENETIC EXPRESSION OF ARYL HYDROCARBON HYDROXYLASE ACTIVITY: EVIDENCE FO
98 HYDROCARBON HYDROXYLASE INDUCTION IN MI/ GENETIC EXPRESSION OF MICROSOMAL ELECTRON TRANSPORT ASSOCIATED WITH ARYL
84 PLACENTAL INDUCTION OF MIXED-FUNCTION OXYGENASES IN EXTRA-HEPATIC TISSUES BY 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN.
84 HEPATIC AND EXTRAHEPATIC METABOLISM OF +-14C-STYRENE OXIDE
93 LORODIBENZO-P-DIOXIN ON THE CAPACITY OF HEPATIC AND EXTRAHEPATIC TISSUES TO CONVERT PROCARCINOGENS TO MUTAGENS
82 AL STIMULATION OF BENZO(A)PYRENE (BP) METABOLISM IN EXTRAHEPATIC MOUSE TISSUES BY 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN(TCDD
87 THE INDUCTION OF SISTER CHROMATID EXCHANGE IN HUMAN FIBROBLASTS BY DIETHYLSTILBESTROL (MEETING ABSTRACT). / STUDIES
100 S./ FOREST WORKERS EXPOSED AND UNEXPOSED TO PHENOXY ACID PREPARATION
93 N OF MONOOXYGENASE ACTIVITIES AND CYTOCHROME P1-450 FORMATION BY 2,3,7,8-TETRACHLORODIBENZO-AND-DIOXIN IN MICE GENETIC
93 OLIC RECEPTOR FOR AN LOCUS. EVIDENCE FOR REGULATORY GENE DYSFUNCTION IN NONRESPONSIVE CELL CULTURES CONTAINING THE R
80 OXYLATION OF 2-ACETYLAMINOFLUORENE AND ACETAMIN/ GENE DYSFUNCTION IN NONRESPONSIVE CELL CULTURES CONTAINING THE R
93 IONE OXIDOREDUCTASE AND MICROSOMAL ARYL HYDROCA/ GENETIC DIFFERENCES IN THE AROMATIC HYDROCARBON-INDUCIBLE M-HYDR
88 SELLA TYPHIMURIUM./ GENETIC DIFFERENCES IN INDUCTION OF CYTOSOL REDUCED-NAD(P)-MENAD
93 (TH ARYL HYDROCARBON HYDROXYLASE INDUCTION IN M/ GENETIC EFFECTS OF CHLORINATED ANILINES AND AZOBENZENES ON SALMO
97 TRACHLORODIBENZO-P-DIOXIN: EVIDENCE FOR A RECEP/ GENETIC EXPRESSION OF MICROSOMAL ELECTRON TRANSPORT ASSOCIATED W
94 DENCE FOR A RECEPTOR MUTATION IN NONRESPONSI/ GENETIC EXPRESSION OF ARYL HYDROCARBON HYDROXYLASE BY 2,3,7,8-TE
85 DUCTION OF MONOOXYGENASE ACTIVITIES AND CYTOCHR/ GENETIC EXPRESSION OF ARYL HYDROCARBON HYDROXYLASE ACTIVITY: EVI
70 OLYCYCLIC AROMATIC COMPOUNDS IN MICE. CO-SEGREG/ GENETIC EXPRESSION OF ARYL HYDROCARBON HYDROXYLASE ACTIVITY. IN
30 A REVIEW OF THE GENETIC REGULATION OF UDP-GLUCURONOSYLTRANSFERASE INDUCTION BY P
25 LCHOLANTHRENE-INITIATED SUBCUTANEOUS TUMORS IN MICE GENETIC TOXICOLOGY OF CHLORINATED DIBENZO-P-DIOXINS.
65 TION BY 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN IN MICE GENETICALLY 'NONRESPONSIVE' AT AN LOCUS. / 2,3,7,8,-TETRACHLORDD
67 BENZO-P-DIOXIN: EVIDENCE FOR A RECEPTOR MUTATION IN GENETICALLY 'NONRESPONSIVE' TO OTHER AROMATIC HYDROCARBONS.
9 THE GENETICALLY NON-RESPONSIVE MICE. / GENETIC EXPRESSION OF ARYL HY
72 NY EFFECT OF 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN ON GENOTOXIC EFFECTS OF 2,4,5-T.
63 STUDIES ON THE REQUIREMENTS FOR INDUCTION OF UDP GLUCURONIDE CONJUGATION OF VARIOUS AGLYCONES. STUDIES IN WISTAR
89 NTHRENE, AND 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN ON GLUCURONOSYL-TRANSFERASE (T-ASE) ACTIVITY IN THE REUBER HEPATOMA
36 ICITY OF 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN IN THE GLUTATHIONE S-TRANSFERASE ACTIVITY OF RAT LIVER CYTOSOL. / THE I
47 ,7,8-TETRACHLORODIBENZO-P-DIOXIN (/ DEPRESSION OF / TOX
GOLDEN SYRIAN HAMSTER.
GUINEA-PIG TESTICULAR MICROSOMAL CYTOCHROME P-450 CONTENT BY 2,3

UCATION OF VARIOUS AGLYCONES. STUDIES IN WISTAR AND
TOXICOPATHOLOGY CHARACTERISTICS OF THE
LABORATORY STUDIES ON THE IMMUNE EFFECTS OF
YL HYDROCARBON HYDROXYLASE ACTIVITY OF TWENTY-THREE
ARCINOGENIC AND OTHER CHRONIC EFFECTS OF PERSISTENT
AMINES TO MUTAGENS BY POSTMITOCHONDRIAL FRACTION OF
,8-TETRACHLORODIBENZO-P-DIOXIN IN THE GOLDEN SYRIAN
HUMAN
IOXIN (TCDD) AT SEVESO, ITALY./
VIETS AND VETS FEAR HERBICIDE
N./
,7,8-TETRACHLORODIBENZO-P-DIOXIN ON THE CAPACITY OF
ATED CHE/ COMPARISON OF INDUCTION PATTERNS OF RAT
INBRED MICE (MEETING ABSTRACT)./
ENDOCRINE INDEPENDENCE./ ONTOGENY OF THE RAT
PROMOTION BY 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN OF
ROLE OF PESTICIDES IN
LOR 1254 AS A PROMOTER OF DIETHYLNITROSAMINE (DENA)
UORENE (AAF) N- AND C-HYDROXYLATION IN ISOLATED RAT
URONOSYLTRANSFERASE ACTIVITY IN THE REUBER H-4-II-E
URONOSYL-TRANSFERASE (T'ASE) ACTIVITY IN THE REUBER
LE NORMAL LIVER AND 2-ACETYLAMINOFLUORENE INDUCIBLE
OF 2-ACETYLAMINOFLUORENE AND ACETAMINOPHEN-PRODUCED
PURE DIOXIN IN SWISS/ CARCINOGENICITY TESTING OF
RESEARCH RELATED TO THE
VIETS AND VETS FEAR
WASHINGTON./
,3,7,8-TETRACHLORDD/ CARCINOGENIC BIOASSAY OF THE
ENOLS (LETTER TO EDITOR)./ MALIGNANT LYMPHOMA OF
PERTIES OF ARYL HYDROCARBON HYDROXYLASE IN A STABLE
ES ON THE INDUCTION OF SISTER CHROMATID EXCHANGE IN
20-P-DIOXIN (TCDD) AT SEVESO, ITALY./
HYDROCARBON HYDROXYLASE IN FRESH MITOGEN-ACTIVATED

TION, INHIBITION, AND BIOLOGICAL PROPERTIES OF ARYL
NAD(P):MENADIONE OXIDOREDUCTASE AND MICROSOMAL ARYL
EVIDENCE FOR A RECEPT/ GENETIC EXPRESSION OF ARYL
ENZO-P-DIOXINS (MEETING ABSTRACT)./ ARYL
ON IN NONRESPONSI/ THE GENETIC EXPRESSION OF ARYL
HIBITION, AND SOME ENZYMOLOGICAL PROPERTIES OF ARYL
TIVITIES AND CYTOCHRO/ GENETIC EXPRESSION OF ARYL
MICROSOMAL ELECTRON TRANSPORT ASSOCIATED WITH ARYL
OS. EVIDENCE FOR STR/ CYTOSOLIC RECEPTOR FOR ARYL
ETRACHLORODIBENZO(P)DIOXIN UPON INHERITANCE OF ARYL
ENOBARBITAL/ TIME COURSE OF THE INDUCTION OF ARYL
HOLANTHRENE / RELATIONSHIP BETWEEN LEVELS OF ARYL
CDD) INDUCED SYNTHESIS OF CYTOCHROME P-448 AND ARYL
3,7,8-TETRACHLORODIBENZO-P-DIOXIN INDUCTION OF ARYL
ROMATIC COMPOUNDS IN MICE. CO-SEGREGATION WITH ARYL
HD ACETAMINO/ GENETIC DIFFERENCES IN THE AROMATIC
D-FUNCTION OXIDASE ACTIVITIES BY VARIOUS POLYCYCLIC
TINE AND LIV/ EFFECTS OF POLYHALOGENATED AROMATIC
MICE GENETICALLY 'NONRESPONSIVE' TO OTHER AROMATIC
ENZO-P-DIOXIN OF SKIN TUMORIGENESIS WITH POLYCYCLIC
SYNTHESIS OF CYTOCHROME P-448 AND ARYL HYDROCARBON
HALOGENATED AROMATIC HYDROCARBONS ON BENZO(A)PYRENE
RELATIONSHIP BETWEEN LEVELS OF ARYL HYDROCARBON
CYTOCHRO/ GENETIC EXPRESSION OF ARYL HYDROCARBON
NS (MEETING ABSTRACT)./ ARYL HYDROCARBON
PONS)/ THE GENETIC EXPRESSION OF ARYL HYDROCARBON
A RECEPT/ GENETIC EXPRESSION OF ARYL HYDROCARBON
TION, AND BIOLOGICAL PROPERTIES OF ARYL HYDROCARBON
HLORODIBENZO-P-DIOXIN INDUCTION OF ARYL HYDROCARBON
D SOME ENZYMOLOGICAL PROPERTIES OF ARYL HYDROCARBON
TIME COURSE OF THE INDUCTION OF ARYL HYDROCARBON
IDNE OXIDOREDUCTASE AND MICROSOMAL ARYL HYDROCARBON
-SEGREGATION WITH ARYL HYDROCARBON BENZO(A)PYRENE
ELECTRON TRANSPORT ASSOCIATED WITH ARYL HYDROCARBON
FOR STR/ CYTOSOLIC RECEPTOR FOR ARYL HYDROCARBON
BENZO(P)DIOXIN UPON INHERITANCE OF ARYL HYDROCARBON
COMPARISON OF
LABORATORY STUDIES ON THE
ORODIBENZO-P-DIOXIN (TCDD) ON PARAMETERS OF VARIOUS
EFFECTS OF ENVIRONMENTAL CONTAMINANTS ON THE
INCREASED
TETRACHLORODIBENZO-RHO-DIOXIN./ INCREASED
TETRACHLORODIBENZO-P-DIOXIN./
F 2,3,7,8-TETRACHLORODIBENZO-RHO-DIOXIN./
F 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN./
3,7,8-TETRACHLORODIBENZO-P-DIOXIN AND ITS ENDOCRINE
OF THE MAJOR CYTOCHROME P-450 FORM TRANSPLACENTALLY
XYLAS/ 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN, DIELDRIN AND OTHER
7,8-TETRACHLORODIBENZO-P-DIOXIN. DIELDRIN AND OTHER
R TEMPORAL CONTROL OF TWO FORMS OF CYTOCHROME P-450
IN INDUCIBLE NORMAL LIVER AND 2-ACETYLAMINOFLUORENE
CAL IDENTITY OF 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN
CYTOSOLIC RECEPTOR FOR ARYL HYDROCARBON HYDROXYLASE
GENETIC REGULATION OF UDP-GLUCURONOSYLTRANSFERASE
REPORT ASSOCIATED WITH ARYL HYDROCARBON HYDROXYLASE
IN ISOLATED RAT HEPATOCYTES (MEETING ABSTRACT)./
VIDENCE FOR / 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN
D MICROSOMES BY PHENOBARBITAL/ TIME COURSE OF THE
TRANSPLACENTAL
CHLORODIBENZO-P-DIOXIN./
VIVO BREATH ANALYSIS (MEETING ABSTRA/ CARCINOGEN
MICROSOMAL ARYL HYDROCAR/ GENETIC DIFFERENCES IN

BY TCDD./
N./
IOUS POLYCYCLIC HYDROCARBONS (MEETIN/ COMPARATIVE
BY 2,3,7,8-TETRACHLORODIBENZO-P-D/ TRANSPLACENTAL
PRESSION OF ARYL HYDROCARBON HYDROXYLASE ACTIVITY.
E REUBER HEPATOM/ STUDIES ON THE REQUIREMENTS FOR
H-4-II-E HEPATOMA CELL CULTURE./
THER POLYPEPTIDES PRODUCED BY AD/ MULTIPLICITY OF
ASES BY PESTICIDES AND RELATED CHE/ COMPARISON OF
ABON HYDROXYLASE IN A STABLE HUMAN B-LYMPHOCYTE/
HYDROCARBON HYDROXYLASE IN FRESH MITOGEN-ACTIV/
WITH ARYL HYDROCARBON BENZO(A)PYRENE HYDROXYLASE
EFFECT OF 2,3,7,8-TETRACHLORODIBENZO(P)DIOXIN UPON
GENESIS WITH POLYCYCLIC HYDROCARB/ TIME-DEPENDENT
YLASE IN A STABLE HUMAN B-LYMPHOCYTE / INDUCTION,
N HYDROXYLASE IN FRESH MITOGEN-ACTIVA/ INDUCTION,
O(A)PYRENE AND 7,12-DIMETHYLBENZ(A)ANTHRACENE TUMOR
COCARCINOGENS - A RECEPTOR REGULATING THE CHEMICAL
IC HYDROCARBONS (MEETIN/ COMPARATIVE INDUCTION OF
ABONS ON BENZO(A)PYRENE HYDROXYLASE ACTIVITY IN THE
GULATING T/ CHARACTERISATION AND REGULATION OF AN
E METABOLISM OF BENZO(A)PYRENE IN RAT TISSUES AFTER

GUNN RATS. / DIFFERENT EFFECT OF 2,3,7,8-TETRACHLORODIBENZO-P-DI
HALOGENATED AROMATICS (MEETING ABSTRACT).
HALOGENATED AROMATICS. / AR
HALOGENATED DIBENZO-P-DIOXINS (MEETING ABSTRACT). / THE C
HALOGENATED ORGANIC COMPOUNDS. / ACTIVATION OF NITROS
HAMSTER PANCREAS. / TOXICITY OF 2,3,7
HAMSTER.
HEALTH EFFECTS FROM ACCIDENTAL RELEASE OF TETRACHLORODIBENZO-P-D
HEALTH EFFECTS. VIETNAMESE OFFICIAL BRINGS CONCERNS TO WASHINGTO
HEPATIC AND EXTRAHEPATIC METABOLISM OF **14C-STYRENE OXIDE.
HEPATIC AND EXTRAHEPATIC MOUSE TISSUES TO CONVERT PROCARCINOGENS
HEPATIC MICROSOMAL MIXED-FUNCTION OXIDASES BY PESTICIDES AND REL
HEPATIC NUCLEAR UPTAKE OF 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN IN
HEPATIC RECEPTOR FOR 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN AND ITS
HEPATOCARCINOGENESIS FROM DIETHYLNITROSAMINE. / QUANTITATIVE EVA
HEPATOCARCINOGENESIS.
HEPATOCARCINOGENESIS IN RATS (MEETING ABSTRACT). / DIBENZOFURAN-
HEPATOCYTES (MEETING ABSTRACT). / INDUCTION OF 2-ACETYLAMINOFL
HEPATOMA CELL CULTURE. / INDUCTION OF UDP-GLUC
HEPATOMA H-4-II-E ESTABLISHED CELL LINE (MEETING ABSTRACT)
HEPATOMA ISOZYMES. / RAT LIVER ALDEHYDE DEHYDROGENASE--IMMUNOCHE
HEPATOTOXICITY IN MICE. / GENETIC DIFFERENCES IN THE AROMATIC HY
HERBICIDE 2,4,5-TRICHLOROPHENOXYETHANOL CONTAINING DIOXIN AND OF
HERBICIDE BUVINOL, ESPECIALLY FOR POSSIBLE CARCINOGENICITY.
HERBICIDE HEALTH EFFECTS. VIETNAMESE OFFICIAL BRINGS CONCERNS TO
HERBICIDE, 2,4,5-TRICHLOROPHENOXYETHANOL (TCPE) WITH DIFFERENT 2
HISTIOCYTIC TYPE AND EXPOSURE TO PHENOXYACETIC ACIDS OR CHLOROPH
HUMAN B-LYMPHOCYTE CELL LINE, RPMI-1788. / INDUCTION, INHIBITION
HUMAN FIBROBLASTS BY DIETHYLSTILBESTROL (MEETING ABSTRACT).
HUMAN HEALTH EFFECTS FROM ACCIDENTAL RELEASE OF TETRACHLORODIBEN
HUMAN LYMPHOCYTES. / INDUCTION, INHIBITION, AND SOME ENZYMOLOGIC

HYDROCARBON HYDROXYLASE IN A STABLE HUMAN B-LYMPHOCYTE CELL LINE
HYDROCARBON HYDROXYLASE IN THE MOUSE. / GENETIC DIFFERENCES IN I
HYDROCARBON HYDROXYLASE BY 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN.
HYDROCARBON HYDROXYLASE ACTIVITY OF TWENTY-THREE HALOGENATED DIB
HYDROCARBON HYDROXYLASE ACTIVITY: EVIDENCE FOR A RECEPTOR MUTATI
HYDROCARBON HYDROXYLASE IN FRESH MITOGEN-ACTIVATED HUMAN LYMPHOC
HYDROCARBON HYDROXYLASE ACTIVITY. INDUCTION OF MONOOXYGENASE AC
HYDROCARBON HYDROXYLASE INDUCTION IN MICE. / GENETIC EXPRESSION
HYDROCARBON HYDROXYLASE INDUCTION BY POLYCYCLIC AROMATIC COMPOUN
HYDROCARBON HYDROXYLASE RESPONSIVENESS. / DEPENDENCE OF THE PORP
HYDROCARBON HYDROXYLASE IN RAT LIVER NUCLEI AND MICROSOMES BY PH
HYDROCARBON HYDROXYLASE ACTIVITY AND SUSCEPTIBILITY TO 3-METHYLC
HYDROCARBON HYDROXYLASE (AHH) ACTIVITY IN FEMALE RAT LIVER (MEET
HYDROCARBON HYDROXYLASE IN FEMALE RAT LIVER. EVIDENCE FOR DE NOV
HYDROCARBON BENZO(A)PYRENE HYDROXYLASE INDUCTION. / GENETIC RE
HYDROCARBON-INDUCIBLE N-HYDROXYLATION OF 2-ACETYLAMINOFLUORENE A
HYDROCARBONS (MEETING ABSTRACT). / COMPARATIVE INDUCTION OF INTE
HYDROCARBONS ON BENZO(A)PYRENE HYDROXYLASE ACTIVITY IN THE INTES
HYDROCARBONS. / GENETIC EXPRESSION OF ARYL HYDROCARBON HYDROXYLA
HYDROCARBONS. / TIME-DEPENDENT INHIBITION BY 2,3,7,8-TETRACHLORD
HYDROXYLASE (AHH) ACTIVITY IN FEMALE RAT LIVER (MEETING ABSTRACT
HYDROXYLASE ACTIVITY IN THE INTESTINE AND LIVER. / EFFECTS OF PO
HYDROXYLASE ACTIVITY AND SUSCEPTIBILITY TO 3-METHYLCHOLANTHRENE
HYDROXYLASE ACTIVITY. INDUCTION OF MONOOXYGENASE ACTIVITIES AND
HYDROXYLASE ACTIVITY OF TWENTY-THREE HALOGENATED DIBENZO-P-DIOXI
HYDROXYLASE ACTIVITY: EVIDENCE FOR A RECEPTOR MUTATION IN NONRES
HYDROXYLASE BY 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN: EVIDENCE FOR
HYDROXYLASE IN A STABLE HUMAN B-LYMPHOCYTE CELL LINE, RPMI-1788.
HYDROXYLASE IN FEMALE RAT LIVER. EVIDENCE FOR DE NOVO SYNTHESIS
HYDROXYLASE IN FRESH MITOGEN-ACTIVATED HUMAN LYMPHOCYTES. / INDU
HYDROXYLASE IN RAT LIVER NUCLEI AND MICROSOMES BY PHENOBARBITAL.
HYDROXYLASE IN THE MOUSE. / GENETIC DIFFERENCES IN INDUCTION OF
HYDROXYLASE INDUCTION. / GENETIC REGULATION OF UDP-GLUCURONOSYLT
HYDROXYLASE INDUCTION IN MICE. / GENETIC EXPRESSION OF MICROSOMA
HYDROXYLASE INDUCTION BY POLYCYCLIC AROMATIC COMPOUNDS. EVIDENCE
HYDROXYLASE RESPONSIVENESS. / DEPENDENCE OF THE PORPHYROGENIC EF
HYPERKERATOSIS INDUCED BY PCBS, PCDF AND PCDD APPLICATION.
IMMUNE EFFECTS OF HALOGENATED AROMATICS.
IMMUNE FUNCTIONS. / INVESTIGATIONS ON THE EFFECTS OF 2,3,7,8-TET
IMMUNE SYSTEM.
INCIDENCE OF NEOPLASMS IN RATS EXPOSED TO LOW LEVELS OF 2,3,7,8-
INCIDENCE OF NEOPLASMS IN RATS EXPOSED TO LOW LEVELS OF 2,3,7,8-
INCREASED INCIDENCE OF NEOPLASMS IN RATS EXPOSED TO LOW LEVELS O
INCREASED INCIDENCE OF NEOPLASMS IN RATS EXPOSED TO LOW LEVELS O
INDEPENDENCE. / ONTOGENY OF THE RAT HEPATIC RECEPTOR FOR 2,
INDUCED IN NEONATAL RABBITS BY 2,3,7,8-TETRACHLORLDIBENZO-P-DIOX
INDUCED SYNTHESIS OF CYTOCHROME P-448 AND ARYL HYDROCARBON HYDRO
INDUCERS. / TIME COURSE OF THE INDUCTION OF ARYL HYDROCARBON HYD
INDUCIBLE BY 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN. / EVIDENCE IN
INDUCIBLE HEPATOMA ISOZYMES. / RAT LIVER ALDEHYDE DEHYDROGENASE-
INDUCIBLE NORMAL LIVER AND 2-ACETYLAMINOFLUORENE INDUCIBLE HEPAT
INDUCTION BY POLYCYCLIC AROMATIC COMPOUNDS. EVIDENCE FOR STRUCTU
INDUCTION BY POLYCYCLIC AROMATIC COMPOUNDS IN MICE. CO-SEGREGATI
INDUCTION IN MICE. / GENETIC EXPRESSION OF MICROSOMAL ELECTRON T
INDUCTION OF 2-ACETYLAMINOFLUORENE (AAF) N- AND C-HYDROXYLATION
INDUCTION OF ARYL HYDROCARBON HYDROXYLASE IN FEMALE RAT LIVER. S
INDUCTION OF ARYL HYDROCARBON HYDROXYLASE IN RAT LIVER NUCLEI AN
INDUCTION OF CARCINOGEN-HYDROXYLATING SYSTEMS WITH 2,3,7,8-TETRA
INDUCTION OF CYTOCHROME-P448-ASSOCIATED ENZYMES: DETECTION BY IN
INDUCTION OF CYTOSOL REDUCED-NAD(P):MENADIONE OXIDOREDUCTASE AND

INDUCTION OF DRUG METABOLIZING ENZYMES IN DIFFERENT RAT TISSUES
INDUCTION OF GT-DIAPHORASE BY 2,3,7,8-TETRACHLORODIBENZO-P-DIOXI
INDUCTION OF INTESTINAL MIXED-FUNCTION OXIDASE ACTIVITIES BY VAR
INDUCTION OF MIXED-FUNCTION OXYGENASES IN EXTRA-HEPATIC TISSUES
INDUCTION OF MONOOXYGENASE ACTIVITIES AND CYTOCHROME P1-450 FORM
INDUCTION OF UDP GLUCURONOSYL-TRANSFERASE (T'ASE) ACTIVITY IN TH
INDUCTION OF UDP-GLUCURONOSYLTRANSFERASE ACTIVITY IN THE REUBER
INDUCTION PATTERNS OF RAT LIVER MICROSOMAL MONO-OXYGENASES AND O
INDUCTION PATTERNS OF RAT HEPATIC MICROSOMAL MIXED-FUNCTION OXID
INDUCTION, INHIBITION, AND BIOLOGICAL PROPERTIES OF ARYL HYDROCA
INDUCTION, INHIBITION, AND SOME ENZYMOLOGICAL PROPERTIES OF ARYL
INDUCTION. / GENETIC REGULATION OF UDP-GLUCURONOSYLTRANSFERASE I
INHERITANCE OF ARYL HYDROCARBON HYDROXYLASE RESPONSIVENESS.
INHIBITION BY 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN OF SKIN TUMORI
INHIBITION, AND BIOLOGICAL PROPERTIES OF ARYL HYDROCARBON HYDROX
INHIBITION, AND SOME ENZYMOLOGICAL PROPERTIES OF ARYL HYDROCARBO
INITIATION AND ITS RELATIONSHIP TO DNA BINDING. / ANTICARCINOGEN
INITIATION OF CANCER (MEETING ABSTRACT). / CHARACTERISATION AND
INTESTINAL MIXED-FUNCTION OXIDASE ACTIVITIES BY VARIOUS POLYCYCL
INTESTINE AND LIVER. / EFFECTS OF POLYHALOGENATED AROMATIC HYDRO
INTRACELLULAR RECEPTOR PROTEIN FOR COCARCINOGENS - A RECEPTOR RE
INTRAGASTRIC ADMINISTRATION OF TCDD. / QUANTITATIVE AND QUALITAT

69 ORODIBENZO-P-DIOXIN (TCDD) RECEPTOR IN RAT LIVER BY
91 LIVER AND 2-ACETYLAMINOFLUORENE INDUCIBLE NEOPLASMA
98 SE OF TETRACHLORODIBENZO-P-DIOXIN (TCDD) AT SEVESO,
110 IBENZOFURANS (PCDFS) FOUND IN YUSHO OIL AND IN USED
17 6-TETRACHLORODIBENZO-P-DIOXIN./
60 YDROCARBON HYDROXYLASE (AHH) ACTIVITY IN FEMALE RAT
61 -TETRACHLORODIBENZO-P-DIOXIN INDUCIBLE NORMA/ RAT
61 ,3,7,8-TETRACHLORODIBENZO-P-DIOXIN INDUCIBLE NORMAL
69 -TETRACHLORODIBENZO-P-DIOXIN (TCDD) RECEPTOR IN RAT
69 DIOXIN ON GLUTATHIONE S-TRANSFERASE ACTIVITY OF RAT
61 CIBLE BY 2,3,7,8-TETRA/ EVIDENCE IN RAT AND MOUSE
59 BY AD/ MULTIPLICITY OF INDUCTION PATTERNS OF RAT
43 RESOLUTION OF TWO FORMS OF CYTOCHROME P-450 FROM
48 NZO-P-DI/ MULTIPLE FORMS OF CYTOCHROME P-450 FROM
48 HE INDUCTION OF ARYL HYDROCARBON HYDROXYLASE IN RAT
93 MBINC OF 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN TO RAT
31 (A)PYRENE HYDROXYLASE ACTIVITY IN THE INTESTINE AND
31 AL, ULTRASTRUCTURAL, AND ENZYMOLOGICAL STUDY OF THE
61 CTION OF ARYL HYDROCARBON HYDROXYLASE IN FEMALE RAT
26 US TUMORS IN MICE GENETICALLY 'NONRESPONSIVE' AT AN
98 CELL CULTURES CONTAIN/ CYTOSOLIC RECEPTOR FOR AN
8 OXIN (TCDD) IN LABORATORY ANIMALS./
65 CARBON HYDROXYLASE IN FRESH MITOGEN-ACTIVATED HUMAN
105 OR CHLOROPHENOLS (LETTER TO EDITOR)./ MALIGNANT
103 ETIC ACIDS OR CHLOROPHENOLS (LETTER TO EDITOR)./
39 COMPARATIVE TOXICOLOGY OF CHLORINATED COMPOUNDS ON
90 UNDS (MEETING ABSTRACT)./ STUDIES ON THE
64 ELOPMENT./
26 AND AROCLOR 1254 ON 7,12-DIMETHYLBENZ A ANTHRACENE
83 TRANSPLACENTAL STIMULATION OF BENZO(A)PYRENE (BP)
84 HEPATIC AND EXTRAHEPATIC
77 EFFECTS OF MICROSOMAL STIMULATORS ON THE IN VITRO
41 DMIN/ QUANTITATIVE AND QUALITATIVE CHANGES IN THE
83 INDUCTION OF DRUG
91 KE OF 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN IN INBRED
26 METHYLCHOLANTHRENE-INITIATED SUBCUTANEOUS TUMORS IN
85 FORMATION BY 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN IN
21 -P-DIOXIN: POTENT ANTICARCINOGENIC ACTIVITY IN CD-1

13 TRACHLORODIBENZO-P-DIOXIN (DIOXIN) CONTENT IN SWISS
14 HANDL CONTAINING DIOXIN AND OF PURE DIOXIN IN SWISS
60 UORENE AND ACETAMINOPHEN-PRODUCED HEPATOTOXICITY IN
56 ATED WITH ARYL HYDROCARBON HYDROXYLASE INDUCTION IN
67 R A RECEPTOR MUTATION IN GENETICALLY NON-RESPONSIVE
65 BENZO A PYRENE-INDUCED CANCERS IN INBRED STRAINS OF
65 EVIDENCE FOR A RECEPTOR MUTATION IN NONRESPONSIVE
70 ERASE INDUCTION BY POLYCYCLIC AROMATIC COMPOUNDS IN
68 CYTOSOL REDUCED-NAD(P):MENADIONE OXIDOREDUCTASE AND
47 O-P-DIOXIN (/ DEPRESSION OF GUINEA-PIG TESTICULAR
56 YDROXYLASE INDUCTION IN MI/ GENETIC EXPRESSION OF
67 COMPARISON OF INDUCTION PATTERNS OF RAT HEPATIC
69 MULTIPLICITY OF INDUCTION PATTERNS OF RAT LIVER
77 ETRACHLORODIPHENYL (TCB), A COMPONENT/ EFFECTS OF
84 RYL HYDROCARBON HYDROXYLASE IN RAT LIVER NUCLEI AND
43 OLUTION OF TWO FORMS OF CYTOCHROME P-450 FROM LIVER
48 MULTIPLE FORMS OF CYTOCHROME P-450 FROM LIVER
96 PROPERTIES OF ARYL HYDROC ON HYDROXYLASE IN FRESH
57 SON OF INDUCTION PATTERNS OF RAT HEPATIC MICROSOMAL
52 BONS (MEETIN/ COMPARATIVE INDUCTION OF INTESTINAL
63 TRACHLORODIBENZO-P-D/ TRANSPLACENTAL INDUCTION OF
59 ICITY OF INDUCTION PATTERNS OF RAT LIVER MICROSOMAL
65 RYL HYDROCARBON HYDROXYLASE ACTIVITY. INDUCTION OF
31 OF 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN IN THE RAT:
100 D PREPARATIONS./
91 O INDUCIBLE BY 2,3,7,8-TETRA/ EVIDENCE IN RAT AND
26 LBENZ A ANTHRACENE METABOLISM AND TUMOR ACTIVITY IN
12 (TCDD) AND AROCHLOR 1254 IN THE TWO-STAGE SYSTEM OF
24 Y OF CERTAIN ENVIRONMENTAL CHEMICALS IN A TWO-STAGE
22 POLYCHLORINATED BIPHENYLS IN A TWO-STAGE SYSTEM OF
KERATINIZATION OF
17 ZO-P-DIOXIN./
68 -DIOXIN ON THE CAPACITY OF HEPATIC AND EXTRAHEPATIC
68 AND MICROSOMAL ARYL HYDROCARBON HYDROXYLASE IN THE
68 O FORMS IN 2-AMINOANTHRACENE AND BENZO ALPHA PYRENE
54 ACTIVATION OF NITROSAMINES TO
65 AHEPATIC MOUSE TISSUES TO CONVERT PROCARCINOGENS TO
67 ETRACHLORODIBENZO-P-DIOXIN: EVIDENCE FOR A RECEPTOR
68 ARBON HYDROXYLASE ACTIVITY: EVIDENCE FOR A RECEPTOR
78 RACT)./ INDUCTION OF 2-ACETYLAMINOFLUORENE (AAF)
60 C DIFFERENCES IN THE AROMATIC HYDROCARBON-INDUCIBLE
54 R PANCREAS./ ACTIVATION OF
91 MICE (MEETING ABSTRACT)./ HEPATIC
56 UCTION OF ARYL HYDROCARBON HYDROXYLASE IN RAT LIVER
27 IN THE RAT./ THE EFFECT OF TOTAL PARENTERAL
97 NZO-P-DIOXIN AND ITS ENDOCRINE INDEPENDENCE./
19 AND OTHER CHRONIC EFFECTS OF PERSISTENT HALOGENATED
83 COMPARATIVE INDUCTION OF INTESTINAL MIXED-FUNCTION
97 N PATTERNS OF RAT HEPATIC MICROSOMAL MIXED-FUNCTION
66 ES IN INDUCTION OF CYTOSOL REDUCED-NAD(P):MENADIONE
63 O-P-D/ TRANSPLACENTAL INDUCTION OF MIXED-FUNCTION
90 NZO-P-DIOXIN (TCDD) INDUCED SYNTHESIS OF CYTOCHROME
44 LIVER. EVIDENCE FOR DE NOVO SYNTHESIS OF CYTOCHROME
47 SION OF GUINEA-PIG TESTICULAR MICROSOMAL CYTOCHROME
45 ,6-TETRAC/ IDENTIFICATION OF THE MAJOR CYTOCHROME
48 SIS (MEETING ABSTRACT)./ THE ROLE OF CYTOCHROME
43 ACHLORODIB/ RESOLUTION OF TWO FORMS OF CYTOCHROME
48 ACHLORODIBENZO-P-DI/ MULTIPLE FORMS OF CYTOCHROME
91 VER FOR TEMPORAL CONTROL OF TWO FORMS OF CYTOCHROME
16 CARCINOGENIC ACTIVITY OF ANALOGUES OF
85 NDUCTION OF MONOOXYGENASE ACTIVITIES AND CYTOCHROME

94 O MUTAGENS BY POSTMITOCHONDRIAL FRACTION OF HAMSTER
37 ZO-P-DIOXIN IN THE RAT./ THE EFFECT OF TOTAL
110 AND (PCDFS) FOUND IN YUSHO OIL AND IN USED JAPANESE
34 COMPARISON OF HYPERKERATOSIS INDUCED BY
34 PARISON OF HYPERKERATOSIS INDUCED BY PCBS, PCDF AND
34 COMPARISON OF HYPERKERATOSIS INDUCED BY PCBS,
110 POLYCHLORINATED DIBENZOFURANS (
64 METABOLIC ACTIVATION/DEACTIVATION REACTIONS DURING
97 P RAT HEPATIC MICROSOMAL MIXED-FUNCTION OXIDASES BY
11 ROLE OF
86 N HYDROXYLASE IN RAT LIVER NUCLEI AND MICROSOMES BY
89 NZO-P-DIOXIN ON GLUTATHIONE S-T/ THE INFLUENCE OF
73 COMPARISON OF
73 THE RAT./
100 ORTALITY OF FOREST WORKERS EXPOSED AND UNEXPOSED TO
105 IGNANT LYMPHOMA OF HISTIOCYTIC TYPE AND EXPOSURE TO

ISOELECTRIC FOCUSING IN POLYACRYLAMIDE GELS. / DETECTION OF THE
ISOZYMES. / RAT LIVER ALDEHYDE DEHYDROGENASE--IMMUNOCHEMICAL IDE
ITALY. / HUMAN HEALTH EFFECTS FROM ACCIDENTAL RELEA
JAPANESE PCB. / POLYCHLORINATED D
KERATINIZATION OF MOUSE TERATOMA CELL LINE X8 PRODUCED BY 2,3,7,
LIVER (MEETING ABSTRACT). / 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN
LIVER ALDEHYDE DEHYDROGENASE--IMMUNOCHEMICAL IDENTITY OF 2,3,7,8
LIVER AND 2-ACETYLAMINOFLUORENE INDUCIBLE NEOPLASMA ISOZYMES.
LIVER BY ISOELECTRIC FOCUSING IN POLYACRYLAMIDE GELS. / DETECTIO
LIVER CYTOSOL. / THE INFLUENCE OF PHENOBARBITAL, 3-METHYLCHOLANT
LIVER FOR TEMPORAL CONTROL OF TWO FORMS OF CYTOCHROME P-450 INDU
LIVER MICROSOMAL MONO-OXYGENASES AND OTHER POLYPEPTIDES PRODUCED
LIVER MICROSOMES OF RABBITS TREATED WITH 2,3,7,8-TETRACHLORODIBE
LIVER MICROSOMES OF RABBITS TREATED WITH 2,3,7,8-TETRACHLORODIBE
LIVER NUCLEI AND MICROSOMES BY PHENOBARBITAL, 3-METHYLCHOLANTHRE
LIVER PROTEIN, RIBOSOMAL RNA, AND DNA. / AN ESTIMATE OF THE MAXI
LIVER. / EFFECTS OF POLYHALOGENATED AROMATIC HYDROCARBONS ON MEN
LIVER. / SHORT-TERM TOXICITY OF 2,3,7,8-TETRACHLORODIBENZO-P-DIO
LIVER. EVIDENCE FOR DE NOVO SYNTHESIS OF CYTOCHROME P-448. / 2,3
LOCUS. / 2,3,7,8,-TETRACHLORODIBENZO-P-DIOXIN AS COCARCINOGEN CA
LOCUS: EVIDENCE FOR REGULATORY GENE DYSFUNCTION IN NONRESPONSIVE
LONG-TERM TOXICOLOGIC STUDIES OF 2,3,7,8-TETRACHLORODIBENZO-P-DI
LYMPHOCYTES. / INDUCTION, INHIBITION, AND SOME ENZYMOLOGICAL PRO
LYMPHOMA OF HISTIOCYTIC TYPE AND EXPOSURE TO PHENOXYACETIC ACIDS
MALIGNANT LYMPHOMA OF HISTIOCYTIC TYPE AND EXPOSURE TO PHENOXYAC
MAMMALIAN SPECIES.
MECHANISM OF THE CHLORINATED DIBENZO-P-DIOXINS AND RELATED COMPO
METABOLIC ACTIVATION/DEACTIVATION REACTIONS DURING PERINATAL DEV
METABOLISM AND TUMOR ACTIVITY IN MOUSE SKIN (MEETING ABSTRACT).
METABOLISM IN EXTRAHEPATIC TISSUES BY 2,3,7,8-TETRACHLORODIBENZO
METABOLISM OF 4-ACETYLAMINOFLUORENE (AAF) BY
METABOLISM OF 4-ALLYL-2-METHYLPHENOL (4A2MP), A COMPONENT O
METABOLISM OF 4-ISOPROPYL-2',3,4,5-TETRACHLOROBIPHENYL (TCB), A COMPONENT O
METABOLISM OF 4-VINYLCYCLOHEXENE OXIDE
METABOLISM OF BENZO(A)PYRENE IN RAT TISSUES AFTER INTRAGASTRIC A
METABOLIZING ENZYMES IN DIFFERENT RAT TISSUES BY TCDD
MICE (MEETING ABSTRACT). / HEPATIC NUCLEAR UPTA
MICE GENETICALLY 'NONRESPONSIVE' AT AH LOCUS. / 3,3',7,8,-TETRACH
MICE GENETICALLY 'NONRESPONSIVE' TO OTHER AROMATIC HYDROCARBONS.
MICE. / 2,3,7,8-TETRACHLORODIBENZO
MICE.

MICE. / CARCINOGENIC BIOASSAY OF TH3 HERBICIDE, 2,4,5-TRICHLOROP
MICE. / CARCINOGENICITY TESTING OF HERBICIDE 2,4,5-TRICHLOROPHEN
MICE. / GENETIC DIFFERENCES IN THE AROMATIC HYDROCARBON-INDUCIBL
MICE. / GENETIC EXPRESSION OF MICROSOMAL ELECTRON TRANSPORT ASSO
MICE. / GENETIC EXPRESSION OF ARYL HYDROCARBON HYDROXYLASE BY 2,
MICE. / RELATIONSHIP BETWEEN LEVELS OF ARYL HYDROCARBON HYDROXYL
MICE. / THE GENETIC EXPRESSION OF ARYL HYDROCARBON HYDROXYLASE A
MICE. CO-SEGREGATION WITH ARYL HYDROCARBON BENZO(A)PYRENE HYDR
MICROSOMAL ARYL HYDROCARBON HYDROXYLASE IN THE MOUSE. / GENETIC
MICROSOMAL CYTOCHROME P-450 CONTENT BY 2,3,7,8-TETRACHLORODIBENZ
MICROSOMAL ELECTRON TRANSPORT ASSOCIATED WITH ARYL HYDROCARBON H
MICROSOMAL MIXED-FUNCTION OXIDASES BY PESTICIDES AND RELATED CHE
MICROSOMAL MONO-OXYGENASES AND OTHER POLYPEPTIDES PRODUCED BY AD
MICROSOMAL STIMULATORS ON THE IN VITRO METABOLISM OF 2,6,2',6'-T
MICROSOMES BY PHENOBARBITAL, 3-METHYLCHOLANTHRENE, 2,3,7,8-TETRA
MICROSOMES OF RABBITS TREATED WITH 2,3,7,8-TETRACHLORODIBENZO-P-
MICROSOMES OF RABBITS TREATED WITH 2,3,7,8-TETRACHLORODIBENZO-P-
MITOGEN-ACTIVATED HUMAN LYMPHOCYTES. / INDUCTION, INHIBITION, AN
MIXED-FUNCTION OXIDASES BY PESTICIDES AND RELATED CHEMICALS.
MIXED-FUNCTION OXIDASE ACTIVITIES BY VARIOUS POLYCYCLIC HYDROCAR
MIXED-FUNCTION OXYGENASES IN EXTRA-HEPATIC TISSUES BY 2,3,7,8-TE
MONO-OXYGENASES AND OTHER POLYPEPTIDES PRODUCED BY ADMINISTRATIO
MONOOXYGENASE ACTIVITIES AND CYTOCHROME P-450 FORMATION BY 2,3,
MORPHOLOGICAL, ULTRASTRUCTURAL, AND ENZYMOLOGICAL STUDY OF THE L
MORTALITY OF FOREST WORKERS EXPOSED AND UNEXPOSED TO PHENOXY ACI
MOUSE LIVER FOR TEMPORAL CONTROL OF TWO FORMS OF CYTOCHROME P-45
MOUSE SKIN (MEETING ABSTRACT). / THE EFFECTS OF 2,3,7,8-TETRACHL
MOUSE SKIN CARCINOGENESIS. / TUMOR-INITIATING ABILITY OF 2,3,7,8
MOUSE SKIN TUMORIGENESIS ASSAY. / LACK OF TUMOR-PROMOTING ABILIT
MOUSE SKIN TUMORIGENESIS: POTENT ANTICARCINOGENIC EFFECTS. / STU
MOUSE TERATOMA CELL LINE X8 PRODUCED BY 2,3,7,8-TETRACHLORODIBEN
MOUSE TISSUES TO CONVERT PROCARCINOGENS TO MUTAGENS FOR SALMONEL
MOUSE. / GENETIC DIFFERENCES IN INDUCTION OF CYTOSOL REDUCED-NAD
MUTAGENESIS (MEETING ABSTRACT). / THE ROLE OF CYTOCHROME P-45
MUTAGENS BY POSTMITOCHONDRIAL FRACTION OF HAMSTER PANCREAS.
MUTAGENS FOR SALMONELLA TYPHIMURIUM AUXOTROPHS. / EFFECTS OF PRE
MUTATION IN GENETICALLY NON-RESPONSIVE MICE. / GENETIC EXPRESSIO
MUTATION IN NONRESPONSIVE MICE. / THE GENETIC EXPRESSION OF ARYL
N- AND C-HYDROXYLATION IN ISOLATED RAT HEPATOCYTES (MEETING ABST
N-HYDROXYLATION OF 2-ACETYLAMINOFLUORENE AND ACETAMINOPHEN-PRODU
NITROSAMINES TO MUTAGENS BY POSTMITOCHONDRIAL FRACTION OF HAMSTE
NUCLEAR UPTAKE OF 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN IN INBRED
NUCLEI AND MICROSOMES BY PHENOBARBITAL, 3-METHYLCHOLANTHRENE, 2,
NUTRITION ON THE TOXICITY OF 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN
ONTOGENY OF THE RAT HEPATIC RECEPTOR FOR 2,3,7,8-TETRACHLORODIBE
ORGANIC COMPOUNDS. / THE CARCINOGENIC
OXIDASE ACTIVITIES BY VARIOUS POLYCYCLIC HYDROCARBONS (MEETING A
OXIDASES BY PESTICIDES AND RELATED CHEMICALS. / COMPARISON OF IN
OXIDOREDUCTASE AND MICROSOMAL ARYL HYDROCARBON HYDROXYLASE IN TH
OXYGENASES IN EXTRA-HEPATIC TISSUES BY 2,3,7,8-TETRACHLORODIBENZ
P-448 AND ARYL HYDROCARBON HYDROXYLASE (AHH) ACTIVITY IN FEMALE
P-448. / 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN INDUCTION OF ARYL H
P-450 CONTENT BY 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN (TCDD) INDE
P-450 FORM TRANSPLACENTALLY INDUCED IN NEONATAL RABBITS BY 2,3,7
P-450 FORMS IN 2-AMINOANTHRACENE AND BENZO ALPHA PYRENE MUTAGENE
P-450 FROM LIVER MICROSOMES OF RABBITS TREATED WITH 2,3,7,8-TETR
P-450 FROM LIVER MICROSOMES OF RABBITS TREATED WITH 2,3,7,8-TETR
P-450 INDUCIBLE BY 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN. / EVIDEN
P-DIMETHYLAMINOAZOBENZENE.
P1-450 FORMATION BY 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN IN MICE

PANCREAS. / ACTIVATION OF NITROSAMINES T
PARENTERAL NUTRITION ON THE TOXICITY OF 2,3,7,8-TETRACHLORODIBEN
PCB. / POLYCHLORINATED DIBENZOFUR
PCBS, PCDF AND PCDD APPLICATION. / COM
PCDD APPLICATION.
PCDF AND PCDD APPLICATION.
PCDFS) FOUND IN YUSHO OIL AND IN USED JAPANESE PCB.
PERINATAL DEVELOPMENT.
PESTICIDES AND RELATED CHEMICALS. / COMPARISON OF INDUCTION PATT
PESTICIDES IN HEPATOCARCINOGENESIS.
PHENOBARBITAL, 3-METHYLCHOLANTHRENE, 2,3,7,8-TETRACHLORODIBENZO-
PHENOBARBITAL, 3-METHYLCHOLANTHRENE, AND 2,3,7,8-TETRACHLORODIBE
PHENOBARBITAL- AND CARCINOGEN-INDUCED ALDEHYDE DEHYDROGENASES IN
PHENOXY ACID PREPARATIONS. / M
PHENOXYACETIC ACIDS OR CHLOROPHENOLS (LETTER TO EDITOR). / MAL

```
89  D) RECEPTOR IN RAT LIVER BY ISOELECTRIC FOCUSING IN
22  -STA/   STUDIES WITH CHLORINATED DIBENZO-P-DIOXINS,
22  ED DIBENZO-P-DIOXINS, POLYBROMINATED BIPHENYLS, AND
33                                  COMPARATIVE TOXICITY OF
77  RACHLOROBIPHENYL (TCB), A COMPONENT OF CARCINOGENIC
110 USED JAPANESE PCB./
10  URRENT INTEREST./
70  ULATION OF UDP-GLUCURONOSYLTRANSFERASE INDUCTION BY
78  EPTOR FOR ARYL HYDROCARBON HYDROXYLASE INDUCTION BY
82  STINAL MIXED-FUNCTION OXIDASE ACTIVITIES BY VARIOUS
20  RACHLORODIBENZO-P-DIOXIN OF SKIN TUMORIGENESIS WITH
42  ASE ACTIVITY IN THE INTESTINE AND LIV/   EFFECTS OF
99  S OF RAT LIVER MICROSOMAL MONO-OXYGENASES AND OTHER
95   INHERITANCE OF ARYL HYDROCARB/   DEPENDENCE OF THE
54                  ACTIVATION OF NITROSAMINES TO MUTAGENS BY
85  ACITY OF HEPATIC AND EXTRAHEPATIC MOU/   EFFECTS OF
95  F HEPATIC AND EXTRAHEPATIC MOUSE TISSUES TO CONVERT
37  TS (MEETING /   DIBENZOFURAN-FREE AROCLOR 1254 AS A
28  OGENESIS FROM DIE/   QUANTITATIVE EVALUATION OF THE
94  ISATION AND REGULATION OF AN INTRACELLULAR RECEPTOR
93  OF 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN TO RAT LIVER
45  OME P-450 FORM TRANSPLACENTALLY INDUCED IN NEONATAL
43   FORMS OF CYTOCHROME P-450 FROM LIVER MICROSOMES OF
48   FORMS OF CYTOCHROME P-450 FROM LIVER MICROSOMES OF
91  OME P-450 INDUCIBLE BY 2,3,7,8-TETRA/   EVIDENCE IN
97   RELATED CHE/   COMPARISON OF INDUCTION PATTERNS OF
97   ITS ENDOCRINE INDEPENDENCE /   ONTOGENY OF THE
78  NOFLUORENE (AAF) N- AND C-HYDROXYLATION IN ISOLATED
60  YL HYDROCARBON HYDROXYLASE (AHH) ACTIVITY IN FEMALE
81  ,7,8-TETRACHLORODIBENZO-P-DIOXIN INDUCIBLE NORM/
89  ,7,8-TETRACHLORODIBENZO-P-DIOXIN (TCDD) RECEPTOR IN
59  O-P-DIOXIN ON GLUTATHIONE S-TRANSFERASE ACTIVITY OF
59  UCED BY AD/   MULTIPLICITY OF INDUCTION PATTERNS OF
56  OF THE INDUCTION OF ARYL HYDROCARBON HYDROXYLASE IN
93  T BINDING OF 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN TO
44  INDUCTION OF ARYL HYDROCARBON HYDROXYLASE IN FEMALE
41  TIVE CHANGES IN THE METABOLISM OF BENZO(A)PYRENE IN
53  INDUCTION OF DRUG METABOLIZING ENZYMES IN DIFFERENT
73  D CARCINOGEN-INDUCED ALDEHYDE DEHYDROGENASES IN THE
36  EXCRETION OF 2,3,7,8-TETRACHLORODIBENZOFURAN IN THE
92  PTOR FOR 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN IN THE
37  ICITY OF 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN IN THE
31  ICITY OF 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN IN THE
27  F DIETHYLNITROSAMINE (DENA) HEPATOCARCINOGENESIS IN
74          DISPOSITION OF TETRACHLORODIBENZOFURAN IN MALE

109         DISPOSITION OF TETRACHLORODIBENZOFURAN IN MALE
4   XIN./              INCREASED INCIDENCE OF NEOPLASMS IN
7   N./                INCREASED INCIDENCE OF NEOPLASMS IN
32  Y OF POLYCHLORINATED BIPHENYLS AND DIBENZOFURANS IN
5   TY STUDY OF 2,3,7,8,-TETRACHLORODIBENZO-P-DIOXIN IN
29   TOXICITY OF 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN IN
72  ON OF VARIOUS AGLYCONES. STUDIES IN WISTAR AND GUNN
93                                  TISSUE DISTRIBUTION OF THE
97  NE INDEPENDENCE./   ONTOGENY OF THE RAT HEPATIC
98  IN NONRESPONSIVE CELL CULTURES CONTAIN/   CYTOSOLIC
78  C AROMATIC COMPOUNDS. EVIDENCE FOR STR/   CYTOSOLIC
89  N OF THE 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN (TCDD)
87  2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN. EVIDENCE FOR A
85  YL HYDROCARBON HYDROXYLASE ACTIVITY. EVIDENCE FOR A
94  CHARACTERISATION AND REGULATION OF AN INTRACELLULAR
94  NTRACELLULAR RECEPTOR PROTEIN FOR COCARCINOGENS - A
98  CTION IN NONRESPONSIVE CELL CULTURES CONTAINING THE
88  OCAR/   GENETIC DIFFERENCES IN INDUCTION OF CYTOSOL
94  LAR RECEPTOR PROTEIN FOR COCARCINOGENS - A RECEPTOR
94  S - A RECEPTOR REGULATING T/   CHARACTERISATION AND
70  C AROMATIC COMPOUNDS IN MICE. CO-SEGREGA/   GENETIC
94                  CYTOSOLIC RECEPTOR FOR AN LOCUS. EVIDENCE FOR
96  LIC AROMATIC COMPOUNDS. EVIDENCE FOR STRUCTURAL AND
82  TION OF UDP-GLUCURONOSYLTRANSFERASE ACTIVITY IN THE
83  OF GLUCURONOSYL-TRANSFERASE (T-ASE) ACTIVITY IN THE
93  8-TETRACHLORODIBENZO-P-DIOXIN TO RAT LIVER PROTEIN,
93  ORODIBENZO-P-DIOXIN TO RAT LIVER PROTEIN, RIBOSOMAL
78  OMOXYLASE IN A STABLE HUMAN B-LYMPHOCYTE CELL LINE,
99   2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN ON GLUTATHIONE
85   EFFECTS OF CHLORINATED ANILINES AND AZOBENZENES ON
85  E TISSUES TO CONVERT PROCARCINOGENS TO MUTAGENS FOR
99  AL RELEASE OF TETRACHLORODIBENZO-P-DIOXIN (TCDD) AT
31  E RAT:  MORPHOLOGICAL, ULTRASTRUCTURAL, AND ENZ/
47  TROL (MEETING ABSTRA/   STUDIES ON THE INDUCTION OF
26  A ANTHRACENE METABOLISM AND TUMOR ACTIVITY IN MOUSE
13   AND AROCHLOR 1254 IN THE TWO-STAGE SYSTEM OF MOUSE
24  ERTAIN ENVIRONMENTAL CHEMICALS IN A TWO-STAGE MOUSE
20  NHIBITION BY 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN OF
22  HLORINATED BIPHENYLS IN A TWO-STAGE SYSTEM OF MOUSE
78  TION BY POLYCYCLIC AROMATIC COMPOUNDS. EVIDENCE FOR
55  COCARCINOGEN CAUSING 3-METHYLCHOLANTHRENE-INITIATED
55  LEVELS OF ARYL HYDROCARBON HYDROXYLASE ACTIVITY AND
13  7,8-TETRACHLORODIBENZO-P-DIOXIN (DIOXIN) CONTENT IN
14  NONYETHANOL CONTAINING DIOXIN AND OF PURE DIOXIN IN
28  P 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN IN THE GOLDEN
108                                 DANGERS OF
77  VITRO METABOLISM OF 2,5,2',5'-TETRACHLOROBIPHENYL (
47  SO CONTENT BY 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN (
12  NG ABILITY OF 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN (
26  NE EFFECTS OF 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN (
99  ACCIDENTAL RELEASE OF TETRACHLORODIBENZO-P-DIOXIN (
5   IC STUDIES OF 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN (
80   HYDROXYLA/   2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN (
40  NE EFFECTS OF 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN (
99  ECTION OF THE 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN (
93  US METABOLIZING ENZYMES IN DIFFERENT RAT TISSUES BY
41  IN RAT TISSUES AFTER INTRAGASTRIC ADMINISTRATION OF
13  Y OF THE HERBICIDE, 2,4,5-TRICHLOROPHENOXYETHANOL (
17  IOXIN./                 KERATINIZATION OF MOUSE
47  HLORODIBENZO-P-DIOXIN (/   DEPRESSION OF GUINEA-PIG

99       HUMAN HEALTH EFFECTS FROM ACCIDENTAL RELEASE OF
108                                 DISPOSITION OF
74                                  DISPOSITION OF
92  ZO-P-DIOXIN IN THE RAT./
41   CHANGES IN THE METABOLISM OF BENZO(A)PYRENE IN RAT
83  CTION OF MIXED-FUNCTION OXYGENASES IN EXTRA-HEPATIC
82  N OF BENZO(A)PYRENE (BP) METABOLISM IN EXTRAHEPATIC
53  CTION OF DRUG METABOLIZING ENZYMES IN DIFFERENT RAT

POLYACRYLAMIDE GELS. / DETECTION OF THE 2,3,7,8-TETRACHLORODIBEN
POLYBROMINATED BIPHENYLS, AND POLYCHLORINATED BIPHENYLS IN A TWO
POLYCHLORINATED BIPHENYLS IN A TWO-STAGE SYSTEM OF MOUSE SKIN TU
POLYCHLORINATED BIPHENYLS AND DIBENZOFURANS IN RATS.
POLYCHLORINATED BIPHENYL MIXTURES (MEETING ABSTRACT). / EFFECTS
POLYCHLORINATED DIBENZOFURANS (PCDFS) FOUND IN YUSHO OIL AND IN
POLYCHLORINATED DIBENZODIOXINS AND DIBENZOFURANS--COMPOUNDS OF C
POLYCYCLIC AROMATIC COMPOUNDS IN MICE. CO-SEGREGATION WITH ARYL
POLYCYCLIC AROMATIC COMPOUNDS. EVIDENCE FOR STRUCTURAL AND REGUL
POLYCYCLIC HYDROCARBONS (MEETING ABSTRACT). / COMPARATIVE INDUCT
POLYCYCLIC HYDROCARBONS. / TIME-DEPENDENT INHIBITION BY 2,3,7,8-
POLYHALOGENATED AROMATIC HYDROCARBONS ON BENZO(A)PYRENE HYDROXYL
POLYPEPTIDES PRODUCED BY ADMINISTRATION OF VARIOUS XENOBIOTICS
PORPHYROGENIC EFFECT OF 2,3,7,8-TETRACHLORODIBENZO(P)DIOXIN UPON
POSTMITOCHONDRIAL FRACTION OF HAMSTER PANCREAS.
PRETREATMENT WITH 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN ON THE CAP
PROCARCINOGENS TO MUTAGENS FOR SALMONELLA TYPHIMURIUM AUXOTROPHS
PROMOTER OF DIETHYLNITROSAMINE (DENA) HEPATOCARCINOGENESIS IN RA
PROMOTION BY 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN OF HEPATOCARCIN
PROTEIN FOR COCARCINOGENS - A RECEPTOR REGULATING THE CHEMICAL I
PROTEIN, RIBOSOMAL RNA, AND DNA. / AN ESTIMATE OF THE MAXIMUM IN
RABBITS BY 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN. / IDENTIFICATION
RABBITS TREATED WITH 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN. / RESO
RABBITS TREATED WITH 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN (MEETI
RAT AND MOUSE LIVER FOR TEMPORAL CONTROL OF TWO FORMS OF CYTOCHR
RAT HEPATIC MICROSOMAL MIXED-FUNCTION OXIDASES BY PESTICIDES AND
RAT HEPATIC RECEPTOR FOR 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN AND
RAT HEPATOCYTES (MEETING ABSTRACT). / INDUCTION OF 2-ACETYLAMI
RAT LIVER (MEETING ABSTRACT). / 2,3,7,8-TETRACHLORODIBENZO-P-DIO
RAT LIVER ALDEHYDE DEHYDROGENASE--IMMUNOCHEMICAL IDENTITY OF 2,3
RAT LIVER BY ISOELECTRIC FOCUSING IN POLYACRYLAMIDE GELS. / DETE
RAT LIVER CYTOSOL. / THE INFLUENCE OF PHENOBARBITAL, 3-METHYLCHO
RAT LIVER MICROSOMAL MONO-OXYGENASES AND OTHER POLYPEPTIDES PROD
RAT LIVER NUCLEI AND MICROSOMES BY PHENOBARBITAL, 3-METHYLCHOLAN
RAT LIVER PROTEIN, RIBOSOMAL RNA, AND DNA. / AN ESTIMATE OF THE
RAT LIVER. EVIDENCE FOR DE NOVO SYNTHESIS OF CYTOCHROME P-448
RAT TISSUES AFTER INTRAGASTRIC ADMINISTRATION OF TCDD. / QUANTIT
RAT TISSUES BY TCDD.                                    /
RAT.                                  / COMPARISON OF PHENOBARBITAL- AN
RAT.                                  / DISPOSITION AND
RAT.                                  / TISSUE DISTRIBUTION OF THE RECE
RAT.          / THE EFFECT OF TOTAL PARENTERAL NUTRITION ON THE TOX
RAT:  MORPHOLOGICAL, ULTRASTRUCTURAL, AND ENZYMOLOGICAL STUDY OF
RATS (MEETING ABSTRACT). / DIBENZOFURAN-FREE AROCLOR 1254 AS A P
RATS (MEETING ABSTRACT).

RATS (MEETING ABSTRACT).
RATS EXPOSED TO LOW LEVELS OF 2,3,7,8-TETRACHLORODIBENZO-RHO-DIO
RATS EXPOSED TO LOW LEVELS OF 2,3,7,8-TETRACHLORODIBENZO-P-DIOXI
RATS.                                   / COMPARATIVE TOXICIT
RATS.     / RESULTS OF A TWO-YEAR CHRONIC TOXICITY AND ONCOGENICI
                                                / CHRONIC
RATS.   (MEETING ABSTRACT).
RATS. / DIFFERENT EFFECT OF 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN
RECEPTOR FOR 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN IN THE RAT
RECEPTOR FOR 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN AND ITS ENDOCRI
RECEPTOR FOR AN LOCUS. EVIDENCE FOR REGULATORY GENE DYSFUNCTION
RECEPTOR FOR ARYL HYDROCARBON HYDROXYLASE INDUCTION BY POLYCYCLI
RECEPTOR IN RAT LIVER BY ISOELECTRIC FOCUSING IN POLYACRYLAMIDE
RECEPTOR MUTATION IN GENETICALLY NON-RESPONSIVE MICE. / GENETIC
RECEPTOR MUTATION IN NONRESPONSIVE MICE. / THE GENETIC EXPRESSIO
RECEPTOR PROTEIN FOR COCARCINOGENS - A RECEPTOR REGULATING THE C
RECEPTOR REGULATING THE CHEMICAL INITIATION OF CANCER (MEETING A
RECEPTOR.  (MEETING ABSTRACT). / CYTOSOLIC RECEPTOR FOR AN LOCUS
REDUCED-NAD(P)-MENADIONE OXIDOREDUCTASE AND MICROSOMAL ARYL HYDR
REGULATING THE CHEMICAL INITIATION OF CANCER (MEETING ABSTRACT).
REGULATION OF AN INTRACELLULAR RECEPTOR PROTEIN FOR COCARCINOGEN
REGULATION OF UDP-GLUCURONOSYLTRANSFERASE INDUCTION BY POLYCYCLI
REGULATORY GENE DYSFUNCTION IN NONRESPONSIVE CELL CULTURES CONTA
REGULATORY VARIANTS AMONG ESTABLISHED CELL CULTURE LINES. / CYTO
REUBER H-4-II-E HEPATOMA CELL CULTURE.                  / INDUC
REUBER HEPATOMA H-4-II-E ESTABLISHED CELL LINE (MEETING ABSTRACT
RIBOSOMAL RNA, AND DNA. / AN ESTIMATE OF THE MAXIMUM IN VIVO COV
RNA, AND DNA. / AN ESTIMATE OF THE MAXIMUM IN VIVO COVALENT BIND
RPMI-1788. / INDUCTION, INHIBITION, AND BIOLOGICAL PROPERTIES OF
S-TRANSFERASE ACTIVITY OF RAT LIVER CYTOSOL. / THE INFLUENCE OF
SALMONELLA TYPHIMURIUM                                  / GENETIC
SALMONELLA TYPHIMURIUM AUXOTROPHS. / EFFECTS OF PRETREATMENT WIT
SEVESO, ITALY.                        / HUMAN HEALTH EFFECTS FROM ACCIDENT
SHORT-TERM TOXICITY OF 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN IN TH
SISTER CHROMATID EXCHANGE IN HUMAN FIBROBLASTS BY DIETHYLSTILBES
SKIN (MEETING ABSTRACT). / THE EFFECTS OF 2,3,7,8-TETRACHLORODIB
SKIN CARCINOGENESIS. / TUMOR-INITIATING ABILITY OF 2,3,7,8-TETRA
SKIN TUMORIGENESIS ASSAY. / LACK OF TUMOR-PROMOTING ABILITY OF C
SKIN TUMORIGENESIS WITH POLYCYCLIC HYDROCARBONS. / TIME-DEPENDEN
SKIN TUMORIGENESIS: POTENT ANTICARCINOGENIC EFFECTS. / STUDIES W
STRUCTURAL AND REGULATORY VARIANTS AMONG ESTABLISHED CELL CULTUR
SUBCUTANEOUS TUMORS IN MICE GENETICALLY 'NONRESPONSIVE' AT AH LO
SUSCEPTIBILITY TO 3-METHYLCHOLANTHRENE AND BENZO A PYRENE-INDUCE
SWISS MICE. / CARCINOGENIC BIOASSAY OF THE HERBICIDE, 2,4,5-TRIC
SWISS MICE. / CARCINOGENICITY TESTING OF HERBICIDE 2,4,5-TRICHLO
SYRIAN HAMSTER.                                         / TOXICITY O
T.C.D.D. (LETTER TO EDITOR)
TCB), A COMPONENT OF CARCINOGENIC POLYCHLORINATED BIPHENYL MIXTU
TCDD) (MEETING ABSTRACT). / DEPRESSION OF GUINEA-PIG TESTICULAR
TCDD) AND AROCHLOR 1254 IN THE TWO-STAGE SYSTEM OF MOUSE SKIN CA
TCDD) AND AROCLOR 1254 ON 7,12-DIMETHYLBENZ A ANTHRACENE METABOL
TCDD) AT SEVESO, ITALY.                 / HUMAN HEALTH EFFECTS FROM
TCDD) IN LABORATORY ANIMALS                             / LONG-TERM TOXICOLOG
TCDD) INDUCED SYNTHESIS OF CYTOCHROME P-448 AND ARYL HYDROCARBON
TCDD) ON PARAMETERS OF VARIOUS IMMUNE FUNCTIONS. / INVESTIGATION
TCDD) RECEPTOR IN RAT LIVER BY ISOELECTRIC FOCUSING IN POLYACRYL
TCDD.                                                   / INDUCTION OF DR
TCDD. / QUANTITATIVE AND QUALITATIVE CHANGES IN THE METABOLISM O
TCPE) WITH DIFFERENT 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN (DIOXIN
TERATOMA CELL LINE H8 PRODUCED BY 2,3,7,8-TETRACHLORODIBENZO-P-D
TESTICULAR MICROSOMAL CYTOCHROME P-450 CONTENT BY 2,3,7,8-TETRAC

TETRACHLORODIBENZO-P-DIOXIN (TCDD) AT SEVESO, ITALY.
TETRACHLORODIBENZOFURAN IN MALE RATS (MEETING ABSTRACT).
TETRACHLORODIBENZOFURAN IN MALE RATS (MEETING ABSTRACT).
TISSUE DISTRIBUTION OF THE RECEPTOR FOR 2,3,7,8-TETRACHLORODIBEN
TISSUES AFTER INTRAGASTRIC ADMINISTRATION OF TCDD. / QUANTITATIV
TISSUES BY 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN. / TRANSPLACENTAL
TISSUES BY 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN(TCDD)  (MEETING A
                                                        / INDU
TISSUES BY TCDD.
```

65 N ON THE CAPACITY OF HEPATIC AND EXTRAHEPATIC MOUSE
5 -DIOXIN IN RATS./ RESULTS OF A TWO-YEAR CHRONIC
66 TETRACHLORODIBENZO-P-DIOXIN: FAILURE TO DEMONSTRATE
37 THE EFFECT OF TOTAL PARENTERAL NUTRITION ON THE
36 RIAN HAMSTER./
31 PHOLOGICAL, ULTRASTRUCTURAL, AND ENZY/ SHORT-TERM
29 NG ABSTRACT)./ CHRONIC
32 COMPARATIVE
6) IN LABORATORY ANIMALS./ LONG-TERM
30 A REVIEW OF THE GENETIC
35 COMPARATIVE
33 ETING ABSTRACT)./
61 H 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN./
63 EPATIC TISSUES BY 2,3,7,8-TETRACHLORODIBE/
62 EXTRAHEPATIC TISSUES BY 2,3,7,8-TETRACHLORODIBE/
45 IDENTIFICATION OF THE MAJOR CYTOCHROME P-450 FORM
24 ING ABILITY OF CERTAIN ENVIRONMENTAL CHEMICALS IN A
12 ORODIBENZO-P-DIOXIN (TCDD) AND AROCHLOR 1254 IN THE
22 NATED BIPHENYLS, AND POLYCHLORINATED BIPHENYLS IN A
5 RACHLORODIBENZO-P-DIOXIN IN RATS./ RESULTS OF A
83 TOM/ STUDIES ON THE REQUIREMENTS FOR INDUCTION OF
70 POUNDS IN MICE. CO-SEGREGA/ GENETIC REGULATION OF
82 TOMA CELL CULTURE./ INDUCTION OF
31 ACHLORODIBENZO-P-DIOXIN IN THE RAT: MORPHOLOGICAL,
91 ETING ABSTRACT)./ HEPATIC NUCLEAR
103 DEADLY LEGACY: DIOXIN AND THE VIETNAM
102 ONCERNS TO WASHINGTON./ VIETS AND
103 DEADLY LEGACY: DIOXIN AND THE
102 VIETS AND VETS FEAR HERBICIDE HEALTH EFFECTS.
102 L BRINGS CONCERNS TO WASHINGTON./
111 AMBIENT
72 RONIDE CONJUGATION OF VARIOUS AGLYCONES. STUDIES IN
109 MORTALITY OF FOREST
17 KERATINIZATION OF MOUSE TERATOMA CELL LINE
89 POLYPEPTIDES PRODUCED BY ADMINISTRATION OF VARIOUS
110 POLYCHLORINATED DIBENZOFURANS (PCDFS) FOUND IN

TISSUES TO CONVERT PROCARCINOGENS TO MUTAGENS FOR SALMONELLA TYP
TOXICITY AND ONCOGENICITY STUDY OF 2,3,7,8,-TETRACHLORODIBENZO-P
TOXICITY AND ONCOGENICITY STUDY OF 2,3,7,8- / 2,3,7,8-
TOXICITY IN TWENTY-THREE CULTURED CELL TYPES.
TOXICITY OF 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN IN THE RAT.
TOXICITY OF 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN IN THE GOLDEN SY
TOXICITY OF 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN IN THE RAT: MOR
TOXICITY OF 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN IN RATS. (MEET)
TOXICITY OF POLYCHLORINATED BIPHENYLS AND DIBENZOFURANS IN RATS.
TOXICOLOGIC STUDIES OF 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN (TCDD
TOXICOLOGIC STUDIES OF 2,3,7,8-TETRACHLORODIBENZO-P-DIOXINS.
TOXICOLOGY OF CHLORINATED DIBENZO-P-DIOXINS.
TOXICOLOGY OF CHLORINATED COMPOUNDS ON MAMMALIAN SPECIES.
TOXICOLOGY OF CHLORINATED COMPOUNDS ON MAMMALIAN SPECIES.
TOXICOPATHOLOGY CHARACTERISTICS OF THE HALOGENATED AROMATICS (ME
TRANSPLACENTAL INDUCTION OF CARCINOGEN-HYDROXYLATING SYSTEMS WIT
TRANSPLACENTAL INDUCTION OF MIXED-FUNCTION OXYGENASES IN EXTRA-H
TRANSPLACENTAL STIMULATION OF BENZO(A)PYRENE (BP) METABOLISM IN
TRANSPLACENTALLY INDUCED IN NEONATAL RABBITS BY 2,3,7,8-TETRACHL
TWO-STAGE MOUSE SKIN TUMORIGENESIS ASSAY. / LACK OF TUMOR-PROMOT
TWO-STAGE SYSTEM OF MOUSE SKIN CARCINOGENESIS. / TUMOR-INITIATIN
TWO-STAGE SYSTEM OF MOUSE SKIN TUMORIGENESIS: POTENT ANTICARCINO
TWO-YEAR CHRONIC TOXICITY AND ONCOGENICITY STUDY OF 2,3,7,8,-TET
UDP GLUCURONOSYL-TRANSFERASE (T-ASE) ACTIVITY IN THE REUBER HEPA
UDP-GLUCURONOSYLTRANSFERASE INDUCTION BY POLYCYCLIC AROMATIC COM
UDP-GLUCURONOSYLTRANSFERASE ACTIVITY IN THE REUBER H-4-II-E HEPA
ULTRASTRUCTURAL, AND ENZYMOLOGICAL STUDY OF THE LIVER. / SHORT-T
UPTAKE OF 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN IN INBRED MICE (ME
VETERAN.
VETS FEAR HERBICIDE HEALTH EFFECTS. VIETNAMESE OFFICIAL BRINGS C
VIETNAM VETERAN.
VIETNAMESE OFFICIAL BRINGS CONCERNS TO WASHINGTON.
VIETS AND VETS FEAR HERBICIDE HEALTH EFFECTS. VIETNAMESE OFFICIA
WATER QUALITY CRITERIA: 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN.
WISTAR AND GUNN RATS. / DIFFERENT EFFECT OF 2,3,7,8-TETRACHLORDD
WORKERS EXPOSED AND UNEXPOSED TO PHENOXY ACID PREPARATIONS.
XB PRODUCED BY 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN.
XENOBIOTICS. / MULTIPLICITY OF INDUCTION PATTERNS OF RAT LIVER M
YUSHO OIL AND IN USED JAPANESE PCB.

AUTHOR INDEX

AUTHOR	ABSTRACT NUMBERS
Aitio A.	41, 53, 72
Allen JR.	7, 8, 27, 29, 35, 77
Atlas SA.	25
Azum-Gelade MC.	31
Baars AJ.	69
Barnard SD.	5
Barnes JM.	101
Bates RR.	3
Beatty P.	71
Ben-Zvi Z.	84
Bence J.	13, 14, 15
Bend JR.	84
Berry D L.	21
Berry DL.	12, 20, 22, 23, 24, 26, 61, 62, 63, 85
Beversluis M.	54
Beyer JE.	5
Birnbaum LS.	74, 75, 106
Blumberg WE.	107
Blumer JL.	58
Bracken WM.	23, 24, 63
Bradlaw JA.	80
Breimer DD.	69
Brown EV.	16
Buser HR.	110
Cameron RG.	59
Campbell HA.	28
Carcinogenesis Testing Program.	4
Carlstedt-Duke J.	89, 94
Carlstedt-Duke JM.	92, 97
Carreon RM.	5
Clark G.	39
Cohen GM.	23
Crow KD.	104
Csuka O.	11
Dansette PM.	25
Decad GM.	74, 75, 106
Deitrich RA.	81
Dewse CD.	108
DiGiovanni J.	12, 20, 21, 22, 24, 26, 85
Dittenber DA.	5
Eisinger J.	107
Elfstrom G.	89, 97
Environmental Protection Agency.	111
Faith RE.	39, 40
Farber E.	59
Felton JS.	60
Firestone D.	80
Frauson LE.	5
Freedman HJ.	76, 96
Fukuda H.	32
Gara A.	110
Garthoff LH.	80
Gasiewicz TA.	37
Gati E.	11
Gilbert P.	88
Gleason GL.	20, 24
Glover E.	65, 67, 93
Goldsworthy T.	28
Grant WF.	9
Greenlee WF.	90, 91
Griffin MJ.	59
Guenthner TM.	51, 78, 98
Gurka DP.	54
Gurtoo HL.	76, 96
Gustafsson JA.	89, 94, 97
Haenisch FT.	87
Hardell L.	105
Hargraves WA.	35
Hassing JM.	52
Havens MB.	96
Hay A.	18
Hepner GW.	49
Hogberg B.	89, 97
Hogstedt C.	100
Hollenberg PF.	54
Holscher MA.	36, 37
Hsia MT.	35, 77
Huff JE.	30
Humiston CG.	5
Hummel RA.	5
Hurley NE.	80
IARC Working Group.	2
Iyer RP.	23
James MO.	84
Jansen M.	69
Jensen NM.	68
Jerina DM.	25
Joglekar R.	25
Johnson EF.	43, 45, 46, 48
Joly JG.	59
Jones AH.	85
Jones KG.	95
Juchau MR.	12, 21, 22, 24, 26, 61, 62, 63, 85
Kalnins RP.	5
Kende A.	66
Keyes DG.	5
Kim G.	42
Kimbrough RD.	19
King ME.	3
Kishore GS.	20
Kitchin KT.	44, 50
Knutson JC.	17, 86
Kociba RJ.	5, 6
Koivula T.	73
Koivusalo M.	73
Koller LD.	38
Kordes J.	77
Koteen GM.	82
Kouri RE.	25, 55
Kumaki K.	68
Kuratsune M.	34
LaPorte JR.	104
Lalich JJ.	7, 8
Lamartiniere CA.	64
Lareng L.	31
Law FC.	84
Lin FS.	35
Lindahl R.	81
Loprieno N.	30
Lucier GW.	64
Lui EM.	64
Luster MI.	39, 40
Lutz WK.	56
Madhukar BV.	57
Malik N.	82, 83
Manis J.	42
Marinello AJ.	76
Marniemi J.	72
Marselos M.	73
Masuda Y.	34
Mathews HB.	75
Matsumura F.	57
Matthews HB.	74, 106
McConnell EE.	33
Mercier M.	88
Minowada J.	76, 96
Moore RW.	27
Morita M.	32
Muller-Eberhard U.	43, 45, 46, 48
Murray RK.	59
Namkung MJ.	61, 63
National Cancer Institute.	1
Neal RA.	36, 37, 71
Nebert DW.	25, 51, 60, 65, 68, 78, 98
Nisbet IC.	109
Nishizumi M.	34
Norman RL.	45, 46
Oishi S.	32
Olson JR.	36
Owens IS.	25, 70, 82, 83
Paigen B.	96
Park CN.	5
Parker NB.	76, 96
Parkki MG.	41, 53, 72
Peters PG.	47
Pham-Huu-Chanh.	31
Piken E.	49
Piper WN.	47
Pitot HC.	28
Pocchiari, F.	99
Poland A.	17, 28, 66, 67, 86, 90, 91, 93
Poland AP.	65
Poncelet F.	88
Preston BD.	27, 77
Rao MS.	54
Rappe C.	10, 110
Robinson JR.	65
Roper M.	81
Rude TH.	25
Rudiger HW.	87
Ryan AJ.	84
Saint Ruf G.	31
Saint-Ruf G.	88
Scarpelli DG.	54
Schlatter C.	56
Selkirk JK.	23
Seymour JL.	77
Sharma RN.	59
Shefner AM.	3
Shire JG.	68
Silano V.	99
Slaga TJ.	12, 20, 21, 22, 23, 24, 26, 62, 63, 85
Smith CL.	79
Snochowski M.	89
Somfai-Relle S.	11, 13, 14, 15
Stohs SJ.	52
Subbarao V.	54
Sugar J.	11, 13, 14, 15
Sweeney GD.	95
Thomasson WA.	103
Thorgeirsson SS.	60, 79
Tofilon PJ.	47

AUTHOR	ABSTRACT NUMBERS
Torronen R	73
Toth K	11, 13, 14, 15
Truhaut R	31
Uotila P	41
Van Haverbeck G	31
Van Miller JP	7, 8, 27, 29
Viaje A	12
Viviani A	56
Wade CE	5
Wade N	102
Wassom JS	30
Westerlund B	100
Wilson NM	63
Woods JS	44, 50
Zachariah PK	61, 62, 63
Zampieri A	99

*U.S.GOVERNMENT PRINTING OFFICE : 1982 0-561-807/214

U.S. DEPARTMENT OF COMMERCE
National Technical Information Service
5285 Port Royal Road
Springfield Va. 22161

OFFICIAL BUSINESS

Penalty for Private Use $300

PRINTED MATTER

POSTAGE AND FEES PAID
U.S. DEPARTMENT OF COMMERCE
COM-211

THIRD CLASS
BULK RATE

U.S.MAIL

NOTICE OF MAILING CHANGE

☐ Check here if you wish to discontinue receiving this publication.

☐ Check here if your address has changed and you wish to continue receiving this publication. (Be sure to furnish your complete address including zip code.)

Tear off cover with address label still affixed and send to:

Computer Support Center
ICRDB Program
IIT Research Institute
10 West 35th Street
Chicago IL 60616